

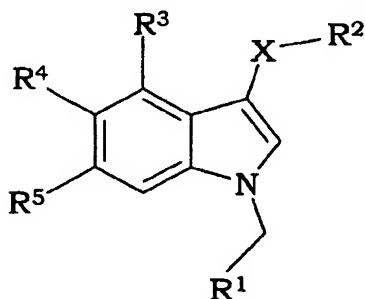
INDOLES USEFUL IN THE TREATMENT OF ANDROGEN-RECEPTOR RELATED DISEASES

The invention relates to indole derivatives, their preparation and their use for the treatment of androgen-receptor related conditions, disorders or diseases and other androgen related treatments.

Compounds possessing androgenic activity are useful in the treatment of men with low endogenous levels of circulating androgenic hormones or men with suppressed androgenic effects. Such treatments are prescribed to older men, to hypogonadal men or men treated with progestagens for male contraception. In addition, potent androgens suppress spermatogenesis and can be used as male contraceptives.

It is thus important to obtain compounds with high affinity for the androgen receptor. Non-steroidal compounds with high affinity for the androgen receptor are particularly useful since they may have different tissue distribution characteristics than steroidal androgens and can be designed by proper choice of substituents to be more or less selective for certain tissues. For example, an action in the brain is usually prevented when compounds are strongly hydrophilic or carry an ionic charge.

The subject invention provides non-steroidal compounds with affinity for the androgen receptor. These compounds are potentially useful for the treatment of androgen-receptor related disorders or disorders which can be treated with androgens. The compounds of the subject invention have a structure according to formula I:



wherein

X is S, SO or SO₂;

R¹ is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, (1C-4C)fluoroalkyl, nitro, (1C-4C)alkyl, (1C-4C)alkoxy or (1C-4C)fluoroalkoxy;

5 R² is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl;

R³ is H, halogen or (1C-4C)alkyl;

R⁴ is H, OH, (1C-4C)alkoxy, or halogen;

R⁵ is H, OH, (1C-4C)alkoxy, NH₂, CN, halogen, (1C-4C)fluoroalkyl, NO₂,

10 hydroxy(1C-4C)alkyl, CO₂H, CO₂(1C-6C)alkyl, or R⁵ is NHR⁶, wherein R⁶ is (1C-6C)acyl optionally substituted with one or more halogens, S(O)₂(1C-4C)alkyl, or S(O)₂aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or

R⁵ is C(O)N(R⁸, R⁹), wherein R⁸ and R⁹ each independently are H, (3C-6C)cycloalkyl, or CH₂R¹⁰, wherein R¹⁰ is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl,

15 (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R⁸ and R⁹ form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl;

20 or a salt or hydrate form thereof.

In one embodiment R¹ is a 5- or 6-membered monocyclic, hetero- or homocyclic, saturated or unsaturated ring structure optionally substituted with one or more substituents selected from the group consisting of halogen, CN, CF₃, nitro, methoxy,

25 trifluoromethoxy or methyl; R² is 2-nitrophenyl, 2-cyanophenyl, 2-hydroxymethyl-phenyl, pyridin-2-yl, pyridin-2-yl-N-oxide, 2-benzamide, 2-benzoic acid methyl ester or 2-methoxyphenyl; R³ is H, halogen or (1C-2C)alkyl; R⁴ is H or F.

In another embodiment R⁵ is H, OH, (1C-4C)alkoxy, CN, halogen, (1C-4C)fluoroalkyl, NO₂, hydroxy(1C-4C)alkyl, CO₂(1C-6C)alkyl, or R⁵ is NHR⁶, wherein R⁶ is (1C-6C)acyl optionally substituted with one or more halogens, S(O)₂(1C-4C)alkyl, or S(O)₂aryl optionally substituted with (1C-4C)alkyl or one or more halogens, or

R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, (3C-6C)cycloalkyl, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-4C)alkylester of carboxy(1C-4C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)-aminocarbonyl, or a 3-, 4-, 5- or 6-membered monocyclic, homo- or heterocyclic, aromatic or non-aromatic ring, or R^8 and R^9 form together with the N a heterocyclic 5- or 6-membered saturated or unsaturated ring optionally substituted with (1C-4C)alkyl.

In yet another embodiment R^3 is H or halogen; R^4 is H; R^5 is H, OH, (1C-4C)alkoxy, CN, F, Cl, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, $CO_2(1C-6C)alkyl$, or R^5 is NHR^6 , wherein R^6 is (1C-3C)acyl optionally substituted with one or more halogens or R^5 is $C(O)N(R^8, R^9)$, wherein R^8 and R^9 each independently are H, (3C-5C)cycloalkyl, or CH_2R^{10} , wherein R^{10} is H, (1C-5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-2C)alkylester of carboxy(1C-2C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, (mono- or di(1C-4C)alkyl)aminomethyl, (mono- or di(1C-4C)alkyl)aminocarbonyl, (3C-5C)cycloalkyl, or a 5-membered heterocyclic ring.

In yet another embodiment X is S or SO_2 ; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-benzamide, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H or F; R^5 is H, OH, (1C-2C)alkoxy, CN, F, Cl, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, $CO_2(1C-4C)alkyl$, or R^5 is NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl, or R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is H, cyclopropyl or R^9 is CH_2R^{10} , wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, methoxy(1C-2C)alkyl, cyclopropyl.

In yet another embodiment X is S; R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, pyrazin-2-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H; R^5 is OH, (1C-2C)alkoxy, CN, CF_3 , NO_2 , hydroxy(1C-4C)alkyl, $CO_2(1C-4C)alkyl$, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, pyrimidin-4-yl, or pyrazin-2-yl; R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R^5 is OH, (1C-2C)alkoxy, CN, hydroxy(1C-4C)alkyl, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

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In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-5-yl, or pyrimidin-4-yl; R^2 is 2-nitrophenyl; R^5 is OH, (1C-2C)alkoxy, CN, or NHR^6 , wherein R^6 is formyl, acetyl, fluoroacetyl, difluoroacetyl, or trifluoroacetyl.

- 10 In a specific embodiment the subject invention provides the compounds 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile-hydrochloride, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole-6-carbonitrile, 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, *N*-[1-(3,5-Difluorobenzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2-fluoro-acetamide, and *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide.
- 15

- In another embodiment X is S; R^1 is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R^2 is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R^3 is H; R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is H, or CH_2R^{10} , wherein R^{10} is H, (1C-2C)alkyl, hydroxy(1C-2C)alkyl, or methoxy(1C-2C)alkyl.
- 20

- 25 In yet another embodiment R^1 is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl; R^2 is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R^5 is $C(O)N(R^8, R^9)$, wherein R^8 is H, and R^9 is CH_2R^{10} , wherein R^{10} is H, or (1C-2C)alkyl.

- In a specific embodiment the subject invention provides the compound 1-(3,5-Difluorobenzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide.
- 30

In yet another embodiment X is S; R¹ is 3,5-difluorophenyl, pyridin-2-yl, pyridin-3-yl, 3-fluorophenyl, 3-cyanophenyl, or 3-nitrophenyl; R² is 2-nitrophenyl, 2-hydroxymethyl-phenyl, 2-methoxyphenyl, 2-cyanophenyl or pyridin-2-yl; R³ is H; R⁵ is C(O)N(R⁸,R⁹), wherein R⁸ and R⁹ each independently are H or CH₂R¹⁰, wherein R¹⁰ is H, (1C-

5 5C)alkyl, (1C-5C)alkenyl, hydroxy(1C-3C)alkyl, (1C-3C)alkoxy(1C-3C)alkyl, or (mono- or di(1C-4C)alkyl)aminomethyl.

In yet another embodiment R¹ is 3,5-difluorophenyl, pyridin-2-yl, or pyridin-3-yl; R² is 2-nitrophenyl, or 2-hydroxymethyl-phenyl; R⁵ is C(O)N(R⁸,R⁹), wherein R⁸ and
10 R⁹ each independently are H, or CH₂R¹⁰, wherein R¹⁰ is H, (1C-5C)alkyl, hydroxy(1C-3C)alkyl, or (1C-3C)alkoxy(1C-3C)alkyl.

In a specific embodiment the subject invention provides the compound 1-(3,5-Difluorobenzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid dimethylamide.

15 In those cases that a compound of the invention contains a basic amine function, the compound may be used as a free base or as a pharmaceutically acceptable salt such as hydrochloride, acetate, oxalate, tartrate, citrate, phosphate, maleate or fumarate.

A compound according to the invention is a compound as defined above, a salt thereof,
20 a hydrate thereof or a prodrug thereof.

The terms used in this description have the following meaning:

alkyl is a branched or unbranched alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, and the like;

25 fluoroalkyl is an alkyl group substituted with one or more fluorine atoms;

cycloalkyl is a cyclized unbranched alkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl and the like;

alkenyl is a branched or unbranched alkenyl group, such as ethenyl, 2-butenyl, etc.;

alkoxy is a branched or unbranched alkyloxy group, for example methyloxy, ethyloxy,

30 propyloxy, isopropyloxy, butyloxy, sec-butyloxy, tert-butyloxy and the like;

fluoroalkoxy is a alkoxy group substituted with one or more fluorine atoms;

aryl is a mono- or polycyclic, homo- or heterocyclic aromatic ring system, such as phenyl, naphthyl or pyridyl; a monocyclic ring with 6 atoms is preferred for use;

acyl is a (substituent-)carbonyl group, such as an aroyl or alkanoyl;

aroyl is arylcarbonyl such as a benzoyl group;
alkanoyl means a formyl or alkylcarbonyl group such as formyl, acetyl and propanoyl;
carboxy is a -COOH substituent, making the compound an organic acid;
carboxylate is a salt of a carboxyl substituent.

- 5 The prefixes (1C-4C), (2C-4C) etc. have the usual meaning to restrict the meaning of the indicated group to those with 1 to 4, 2 to 4 etc. carbon atoms;
halogen refers to fluorine, chlorine, bromine and iodine.

10 The androgen receptor affinity and efficacy of the compounds according to the invention make them suitable for use in the treatment of androgen-receptor related disorders, disorders which can be treated with androgens, and in diagnostic methods focussed on the amount and/or location of androgen receptors in various tissues. For the latter purpose it can be preferred to make labelled variants of the compounds according to the invention. Typical androgen receptor-related treatments are those for male
15 contraception and male or female hormone replacement therapy. Thus the invention also pertains to a method of treatment of androgen insufficiency, by administering to a male or female human or animal an effective amount of any of the compounds of the subject invention. The subject invention also lies in the use of any of its compounds for the preparation of a medicine for treating androgen insufficiency. In the context of the
20 invention, the term "androgen insufficiency" is to be understood to pertain to all kinds of diseases, disorders, and symptoms in which a male or a female suffers from too low a testosterone level, such as in hypogonadal men or boys. In particular, the androgen insufficiency to be treated by a compound of the invention is the reduction of the testosterone level which a male individual incurs as a result of age (the compound of the
25 invention is then used for male hormone replacement therapy), or when he is subject to male contraception. In the context of male contraception, the compound of the invention especially serves to neutralise the effect of regimens of male hormone contraception in which a sterilant such as a progestagen or LHRH (luteinizing hormone releasing hormone) is administered regularly, *e.g.* daily, or it is used as the sole male
30 contraceptive substance.

Thus, the subject invention provides any one of the compounds of the subject invention for use in therapy.

35 The subject invention further encompasses a pharmaceutical composition comprising a compound of the subject invention and a pharmaceutically acceptable carrier. In an embodiment of the subject invention, the pharmaceutical composition is for the

treatment of a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency.

5 The subject invention further provides a use of a compound of the invention for the manufacture of a medicament for the treatment of androgen-receptor related disorders, androgen related disorders and androgen insufficiency.

10 The subject invention further envisions a method of treating a disorder selected from the group consisting of an androgen-receptor related disorder, an androgen related disorder and androgen insufficiency comprising administering a pharmaceutically effective amount of a compound according to the invention to a subject in need thereof.

15 The compounds of the invention may further be useful for the treatment of osteoporosis, as well as other bone disorders, bone fraction repair, sarcopenia, frailty, skin aging, male hypogonadism, female sexual dysfunction, postmenopausal symptoms, atherosclerosis, aplastic anemia, muscular atrophy, lipodystrophy, reduced muscle strength and function, side effects of chemotherapy, chronic fatigue syndrome, benign prostate hyperplasia (BPH), cachexia, chronic catabolic state, cognitive impairment, male contraception, and others.

20 The compounds of the invention may be administered in conjunction with estrogens, progestogen and other androgens.

25 The compounds of the invention can be produced by various methods known in the art of organic chemistry in general. More specifically the routes of synthesis as illustrated in the following schemes and examples can be used. In the schemes and examples the following abbreviations were used:

DMF = dimethylformamide

mCPBA = *meta* chloro perbenzoic acid

30 THF = tetrahydrofuran

TBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

DIPEA = diisopropylethylamine

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

HOBt = 1-hydroxybenzotriazole

NMM = N-methylmorpholine

SPE = solid phase extraction

RP-SPE = reversed phase solid phase extraction

5 DMSO = dimethylsulfoxide

DCM = dichloromethane

DHT = 5 α -dihydrotestosterone

NMP = 1-methyl-2-pyrrolidinone

DMS = dimethyl sulfide

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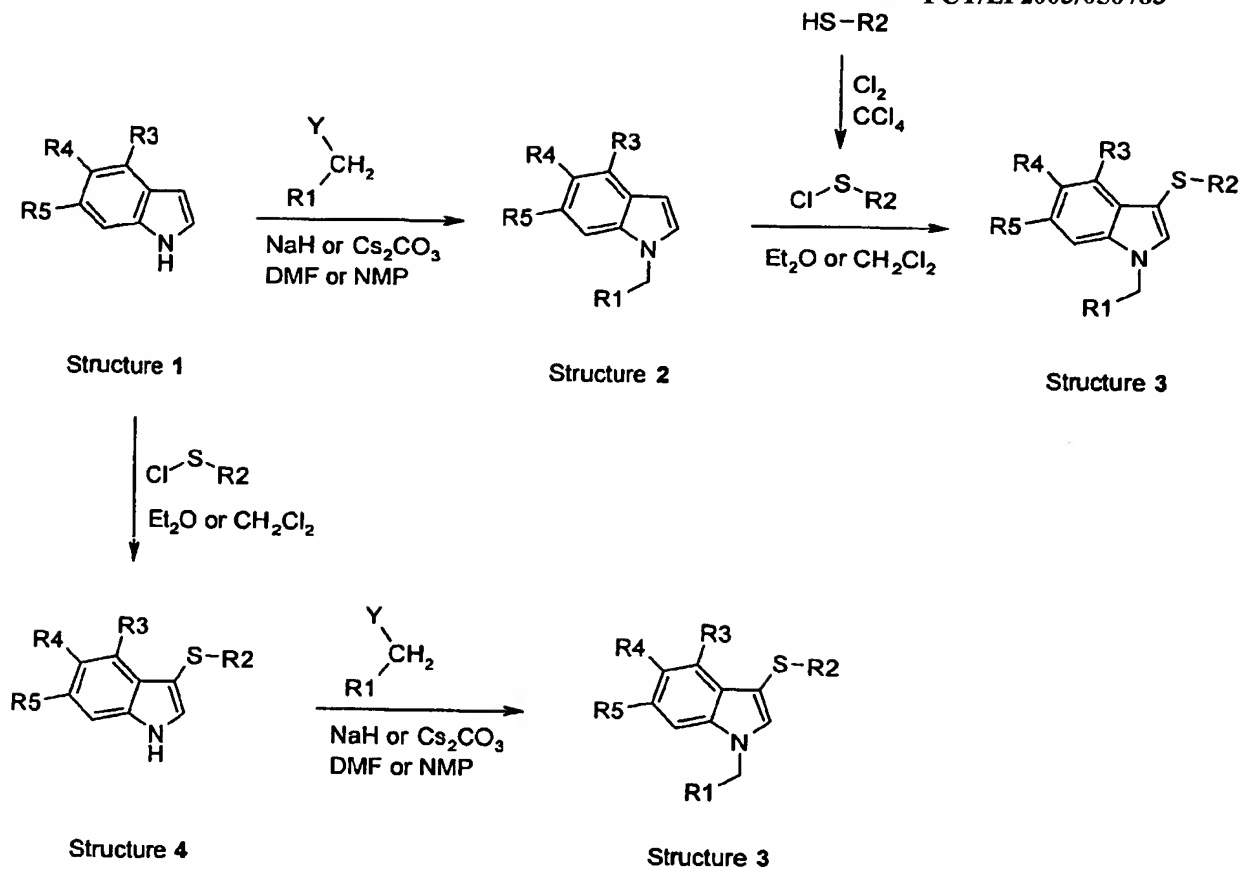
With regard to nomenclature the following trivial names are used interchangeably for substituents R¹ and R²:

	<u>Trivial name</u>	<u>Official name</u>
	2-pyridyl	pyridin-2-yl
15	3-pyridyl	pyridyl-3-yl
	4-pyridyl	pyridyl-4-yl
	3,5-pyrimidyl	pyrimidin-5-yl
	2,4-pyrimidyl	pyrimidin-4-yl
	2,5-pyrazyl	pyrazin-2-yl
20	etc.	

In each of the Schemes I-VII the meanings of the symbols correspond to the definitions given in the previous paragraphs.

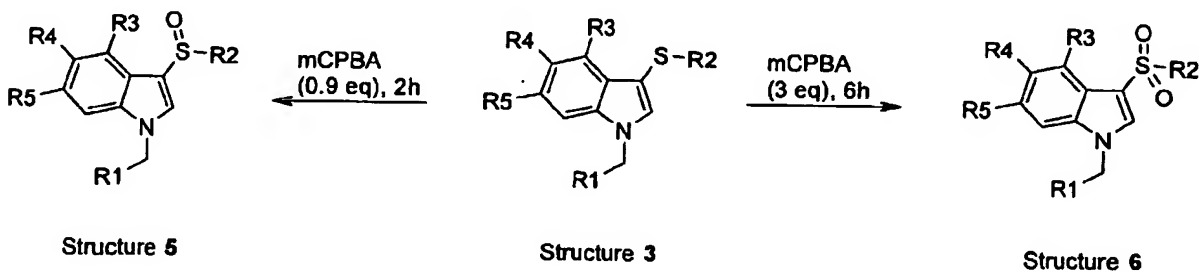
25 Substituted indole compounds of structure 3 were prepared in two steps from the correctly substituted indoles of structure 1, via two different routes. In the first route a correctly substituted indole of structure 1 is N-alkylated with a halide of type R¹CH₂Y, where Y is a halogen, mesylate or tosylate, with NaH or Cs₂CO₃ as a base in DMF or NMP at 0°C to room temperature, to give a compound of structure 2. Structure 2 is then
30 sulfanylated at the C-3 position of the indole ring by reaction with a sulfenyl chloride in either CH₂Cl₂ or diethyl ether at room temperature, to give structure 3. In the second route the two steps of the first route are reversed: the correctly substituted indole of structure 1 is first sulfanylated at the C-3 position of the indole to give structure 4, followed by N-alkylation with R¹CH₂Y to give structure 3 (Scheme I).

35



Scheme I

- 5 Sulfoxides of structure 5 can be obtained by oxidation of the corresponding sulfide (Structure 3) by reaction with e.g. 0.9 equivalents of mCPBA. Sulfones of structure 6 can be obtained by oxidation of the corresponding sulfide (Structure 3) by reaction with e.g. 3 equivalents of mCPBA (Scheme II).

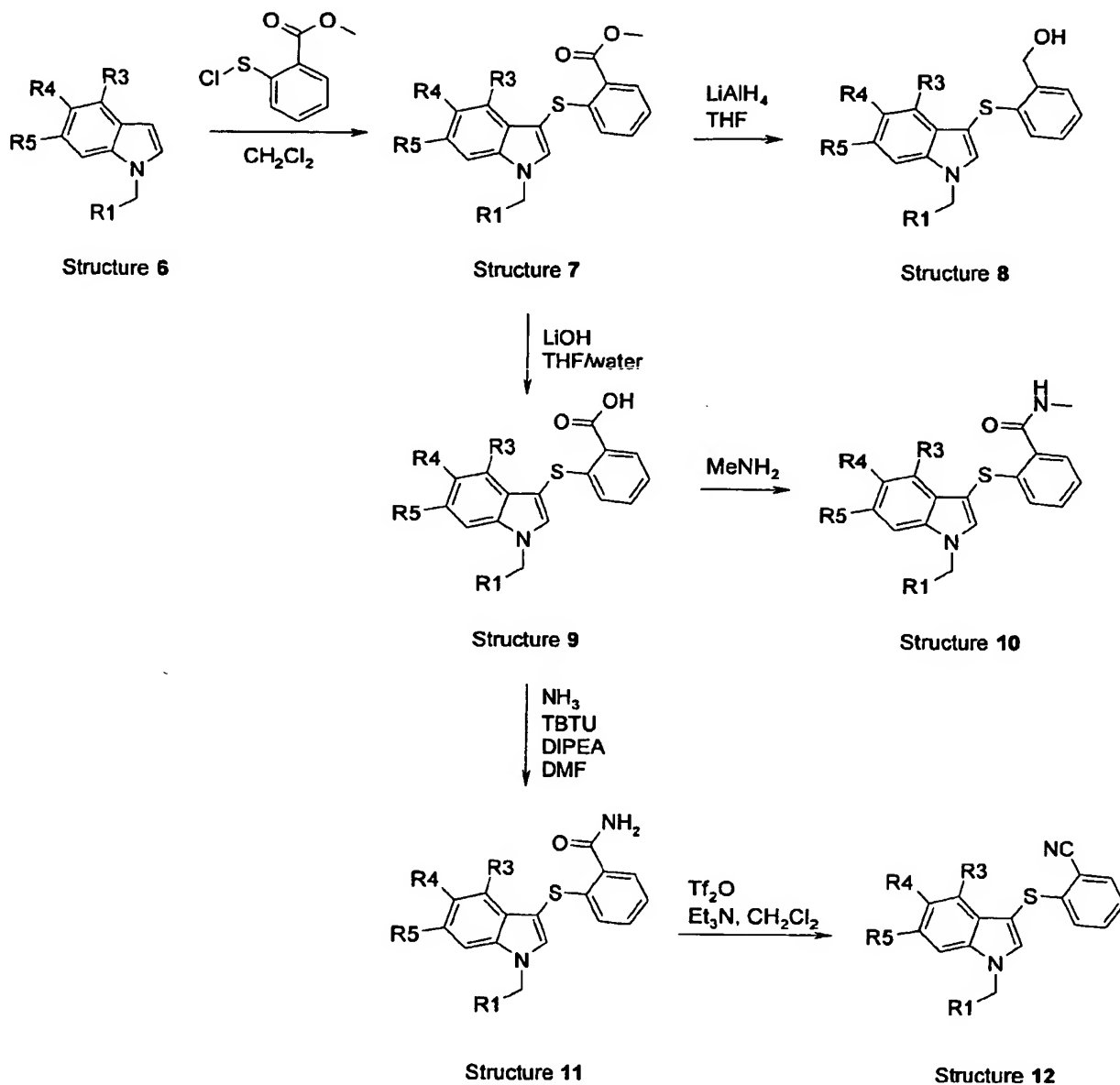


Scheme II

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Scheme III describes the synthesis of compounds of structure 3, in which the R^2 group is a phenyl ring substituted on the 2-position with either CO_2Me (Structure 7), CH_2OH

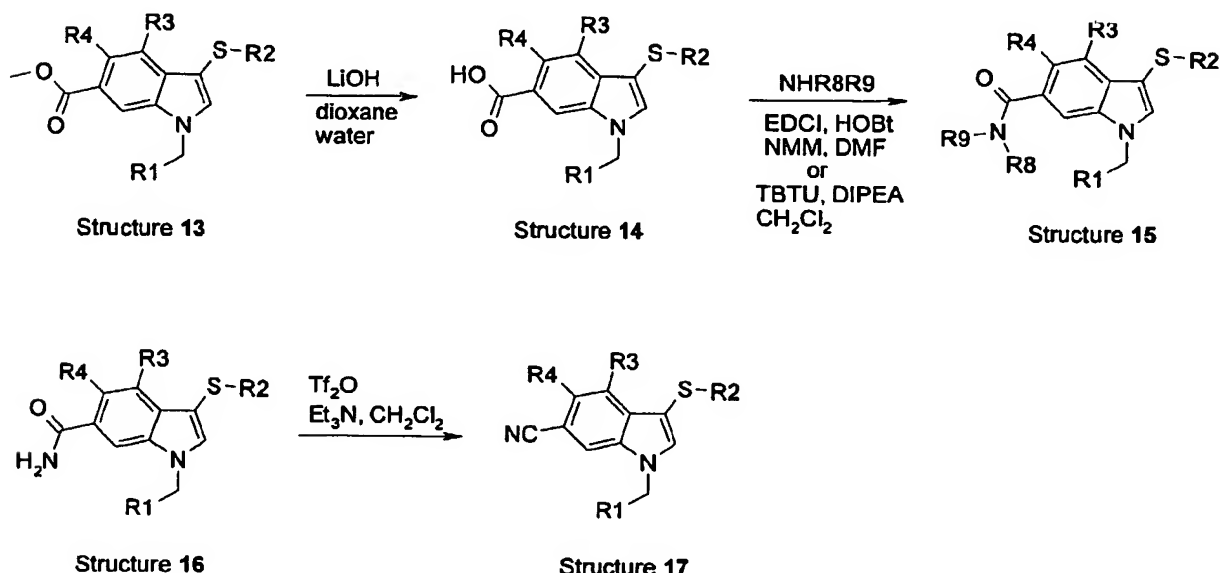
(Structure 8), CO₂H (Structure 9), CONHMe (Structure 10), CONH₂ (Structure 11) or CN (Structure 12).



Scheme III

In the first step a substituted indole of structure 6 is sulfanylated at the 3-position with 2-(carboxymethyl)-phenylsulfenyl chloride, which was prepared from methylthiosalicylate and chlorine gas, to give a compound of structure 7. Reduction of the methyl ester moiety of compounds of structure 7 with LiAlH₄ gave the corresponding hydroxymethyl compounds of structure 8. Saponification of the methyl

ester moiety of compounds of structure 7 with lithium hydroxide gave the corresponding carboxylic acid compounds of structure 9. The carboxylic acid moiety of compounds of structure 9 can be converted to the corresponding carboxamide by reaction with an amine, TBTU and DIPEA in DMF at room temperature. By this method structure 10 was obtained when methylamine was used as the amine and structure 11 was obtained when NH₃ was used as the amine. Dehydration of the benzamide moiety of structure 11 with Tf₂O and triethylamine in CH₂Cl₂ afforded the corresponding benzonitrile compound of structure 12 (Scheme III).

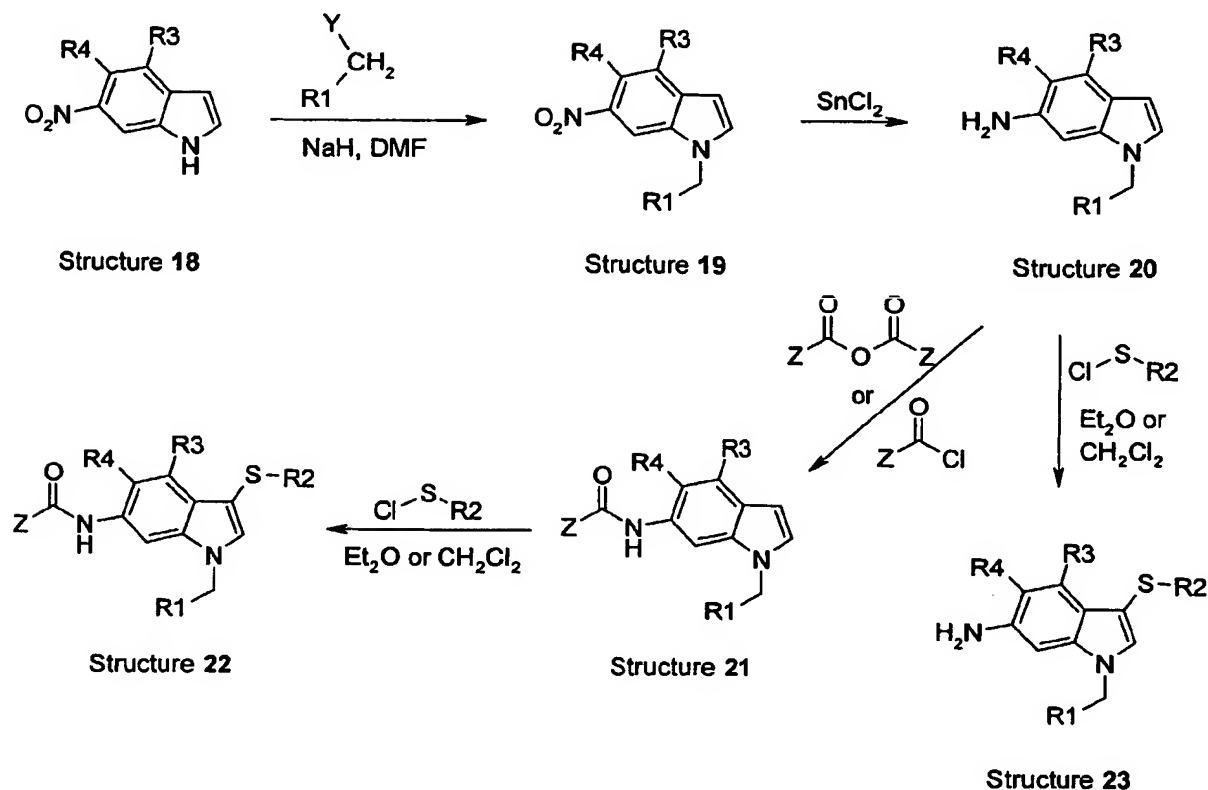


Scheme IV

Scheme IV describes the synthesis of compounds of structure 3, in which the indole ring is substituted at the 6-position with either CO₂Me (Structure 13), CO₂H (Structure 14), CONR⁸R⁹ (Structure 15), CONH₂ (Structure 16) or CN (Structure 17).

Saponification of the methyl ester moiety of structure 13 with lithium hydroxide afforded the corresponding carboxylic acid of structure 14. The carboxylic acid moiety of structure 14 can be converted to the corresponding carboxamides of structures 15 and 16 by reaction with an amine or amine salt, in the presence of EDCI and HOBT in a mixture of NMM and DMF or in the presence of TBTU and DIPEA in CH₂Cl₂ at room temperature. Dehydration of the benzamide moiety of structure 16 with Tf₂O and

triethylamine in CH_2Cl_2 afforded the corresponding benzonitrile compound of structure 17 (Scheme IV).

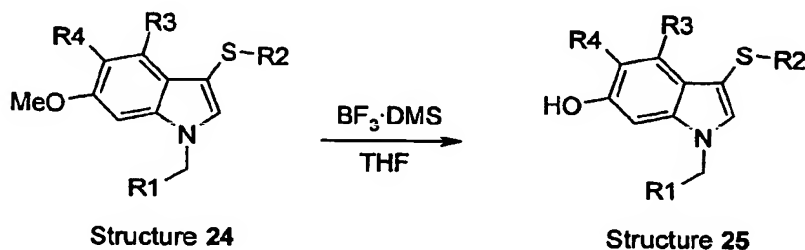


Scheme V

Scheme V describes the synthesis of compounds of structure 22 containing an acylated amine functionality on the 6-position of the indole ring. These compounds can be synthesised from 6-nitro indoles of structure 18 in 4 steps. In the first step the indole of structure 18 is alkylated on the nitrogen atom by reaction of a halide of type $\text{R}^1\text{CH}_2\text{Y}$, in which Y is halogen, mesylate or tosylate, with NaH as a base in DMF to give compounds of structure 19. In the second step the nitro group of structure 19 is reduced to an amine group by SnCl_2 to give structure 20. Subsequent acylation of the amine group with an acid chloride of type ZCOCl afforded structure 21, which was then sulfanylated at the 3-position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or Et_2O as a solvent, at room temperature, to give compounds of structure

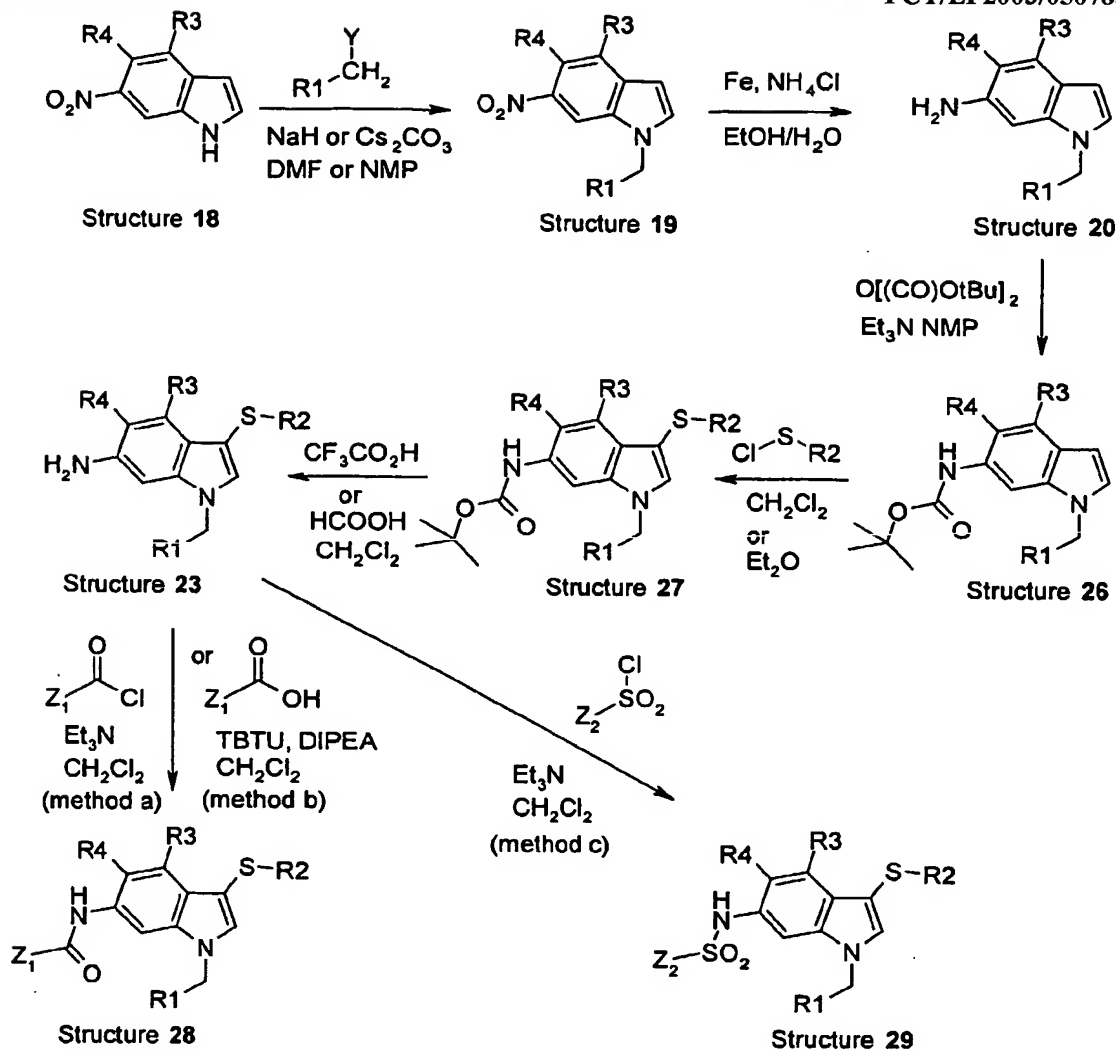
22. Direct sulfanylation of a compound of structure 20 with a sulfenyl chloride afforded structure 23

In Scheme VI is described how methyl ethers of structure 24 can be cleaved with e.g. $\text{BF}_3 \cdot \text{DMS}$ in THF at room temperature to hydroxy compounds of structure 25.



Scheme VI

Scheme VII describes the synthesis of compounds containing either an acylated amine functionality (structure 28) or a sulfonamide functionality (structure 29) at the 6-position of the indole ring. These compounds can be prepared from 6-nitro indoles of structure 18 in 6 steps. In the first step the indole of structure 18 is alkylated on N-1 by reaction of a halide of type $\text{R}^1\text{CH}_2\text{Y}$, in which Y is a halogen, mesylate or tosylate, with NaH or Cs_2CO_3 as a base in either NMP or DMF to give compounds of structure 19. In the second step the nitro group of structure 19 is reduced to an amine group with Fe and NH_4Cl in an ethanol/water mixture to give structure 20. Subsequent acylation of the amine group with di-*tert*-butyl dicarbonate afforded structure 26 which was then sulfanylated at the 3-position of the indole ring by reaction with a sulfenyl chloride in either CH_2Cl_2 or Et_2O to give compounds of structure 27. Then the amide functionality at the 6-position of the indole was cleaved with trifluoroacetic acid or HCOOH to give amines of structure 23. These amines can be converted into amides of structure 28 by reaction with either triethylamine and an acid chloride in CH_2Cl_2 (method a) or an acid, TBTU and DIPEA in CH_2Cl_2 (method b). Sulfonamides of structure 29 can be prepared by reaction of amines of structure 23 with sulfonyl chlorides (method c).



Scheme VII

- 5 The present invention also relates to a pharmaceutical composition comprising the non-steroidal compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro *et al*, *Remington: The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing). Suitable
- 10 auxiliaries are made available in e.g. the Handbook of Pharmaceutical Excipients (2nd Edition, Editors A. Wade and P.J. Weller; American Pharmaceutical Association; Washington; The Pharmaceutical Press; London, 1994). The mixture of a compound according to the invention and a pharmaceutically acceptable auxiliary may be

compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of
5 conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

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Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

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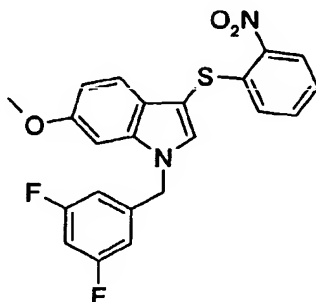
The dosage amounts of the present compounds will be of the normal order for pharmaceutically active compounds, e.g. of the order of 0.001 to 50 mg/kg body weight of the recipient per administration. The recipient can be a human or an animal in need of an androgen receptor-related treatment or an androgen treatment.

The invention is illustrated by the following examples.

Examples

Example 1

- 5 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1H-indole (Compound 63, Structure 3 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^5=OMe$)



- 10 **General method 1:** N-alkylation of a (un)substituted indole of structure 1 to give N-alkylated indole of structure 2, followed by 3-sulfanylation to give substituted indoles of structure 3 (Scheme I).

- (a) 1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indole (Structure 2 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

- 15 Under a nitrogen atmosphere: to a cooled (0°C) solution of 6-methoxyindole (863 mg, 5.86 mmol) in DMF (40 mL) was added NaH (60% in oil; 281 mg, 7.03 mmol) in small portions over a 3 minute period. The resulting green suspension was stirred at 0°C for 10 min. Then 3,5-difluorobenzyl bromide (0.91 mL, 7.03 mmol) was added. The mixture was stirred at 0°C for 1 h and then at room temperature for another 21 h. Ethyl acetate (50 mL) was added and the mixture was washed with 3% aqueous citric acid (3x50 mL) and brine (50 mL). The organic phase was dried (MgSO₄) and concentrated *in vacuo* to give a green oil (1.43 g). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil (1.23 g, yield = 77%).
- 20
- 25 LCMS: 4.01 min (96.3%, $MH^+ = 274$); TLC (ethyl acetate/heptane 1:4): $R_f = 0.46$; ¹H NMR (CDCl₃): δ 3.80 (s, 3H, OCH₃), 5.24 (s, 2H, NCH₂Ar), 6.51 (dd, 1H, $J_1 = 3.5$ Hz,

J2 = 0.8 Hz), 6.57-6.60 (m, 2H), 6.65 (d, 1H, J = 3.1 Hz), 6.66-6.72 (m, 1H), 6.81 (dd, 1H, J1 = 8.6 Hz, J2 = 3.1 Hz), 7.01 (d, 1H, J = 3.5 Hz), 7.53 (d, 1H, J = 8.6 Hz).

(b) 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1H-indole

- 5 (Compound 63, Structure 3 of Scheme I, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁵=OMe)

- 10 To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indole (900 mg, 3.29 mmol) in diethyl ether (20 mL) was added dropwise at room temperature a suspension of 2-nitrobenzenesulfonyl chloride (627 mg, 3.31 mmol) in diethyl ether (10 mL) over a period of 2 min. After stirring at room temperature for 1 h ethyl acetate (50 mL) was added and the mixture was washed with saturated NaHCO₃ solution (2x50 mL) and brine (50 mL). The organic phase was dried (MgSO₄) and concentrated *in vacuo* to give an orange-red oil (1.54 g). The crude product was crystallised from toluene/acetone to give the title compound as orange-red crystalline solid (900 mg, yield = 64%).
- 15 LCMS: 4.25 min (100%, MH⁺ = 427); HPLC: 4.86 min (98.7%); ¹H NMR (CDCl₃): δ 3.82 (s, 3H, OCH₃), 5.32 (s, 2H, NCH₂Ar), 6.63-6.69 (m, 2H), 6.72-6.79 (m, 1H), 6.75 (d, 1H, J = 2.7 Hz), 6.85 (dd, 1H, J1 = 8.2 Hz, J2 = 2.7 Hz), 6.98 (dd, 1H, J1 = 6.7 Hz, J2 = 1.2 Hz), 7.16-7.20 (m, 1H), 7.26-7.30 (m, 1H) 7.34 (s, 1H), 7.39 (d, 1H, J = 8.2 Hz), 8.27 (dd, 1H, J1 = 8.2 Hz, J2 = 1.6 Hz).

According to General method 1 the following compounds were prepared:

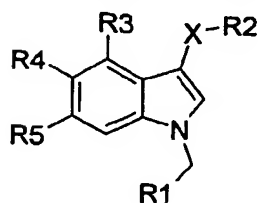


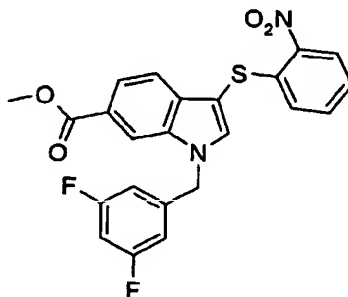
Table 1 Compounds synthesised according to General Method 1

Compound number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt	LCMS	LCMS
								(MH ⁺)	ret. Time ^a (min)
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	411.47	446 ^c	5.14 ^b
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	475.32	476	4.89
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF ₃	464.41	465	5.34 ^b
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH ₂ OH	426.44	Nd	3.88 ^b
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	430.86	431	4.89
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	414.40	415	4.79
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	414.40	415	4.72
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	396.41	397	4.22
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	414.40	415	4.75
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	430.86	431	5.14 ^b
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	410.44	411	5.24 ^b
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	412.41	413	4.50 ^b
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO ₂	441.41	442	4.7
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	412.41	413	4.54 ^b
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.45	274 ^d	4.01
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	398.43	399	3.96
90	S	phenyl	2-nitrophenyl	H	H	H	360.43	361	4.19
91	S	phenyl	2-nitrophenyl	H	OMe	H	390.46	391	4.14
92	S	phenyl	2-nitrophenyl	H	H	OMe	390.46	391	4.12

5 a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used. c) M+Cl. nd = not detected. d) $[M-S(PhNO_2)]H^+$.

Example 2

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (Compound 31, Structure 3 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = CO_2Me$)



(a) 1*H*-Indole-6-carboxylic acid methyl ester (Structure 1 of Scheme I, where $R^3 = R^4 = H$, $R^5 = CO_2Me$)

To a solution of 1*H*-Indole-6-carboxylic acid (1.500 g, 9.31 mmol) in methanol (50 mL) was added concentrated H_2SO_4 (550 μ L, 10.24 mmol). The mixture was stirred overnight at reflux temperature. The mixture was then neutralised to pH 7 by addition of saturated aqueous $NaHCO_3$ and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as green/yellow crystals (688 mg, yield = 53%)

1H NMR ($CDCl_3$): δ 3.94 (s, 3H, CH_3OCO), 6.60 (m, 1H), 7.37 (t, 1H, $J = 4.7$ Hz), 7.66 (d, 1H, $J = 8.2$ Hz), 7.82 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 8.18 (s, 1H), 8.73 (s, 1H, NH)

(b) 1-(3,5-Difluoro-benzyl)-1*H*-indole-6-carboxylic acid methyl ester (Structure 2 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^3 = R^4 = H$, $R^5 = CO_2Me$)

Under a nitrogen atmosphere: to a solution of 1*H*-indole-6-carboxylic acid methyl ester (367 mg, 2.09 mmol) in DMF (10 mL) was added NaH (60% in oil, 101 mg, 2.52 mmol) at room temperature. After stirring for 15 min 1-bromomethyl-3,5-difluorobenzene (325 μ L, 2.51 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with 3% aqueous citric acid (10 mL)

and ethyl acetate (30 mL) was added. The mixture was washed with 3% aqueous citric acid (3x20 mL) and brine (20 mL). The organic phase was dried (MgSO₄) and concentrated *in vacuo* to give a pale yellow oil (702 mg). The crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:9) to give the title compound as a colourless oil, which slowly crystallised on standing (530 mg, yield = 84%).

LCMS: 4.08 min (99%, MH⁺ = 302); ¹H NMR (CDCl₃): δ 3.92 (s, 3H, CO₂CH₃), 5.37 (s, 2H, NCH₂Ar), 6.54-6.60 (m, 2H), 6.64 (d, 1H, J = 3.1 Hz), 6.67-6.74 (m, 1H), 7.27 (d, 1H, J = 3.1 Hz), 7.68 (d, 1H, J = 8.6 Hz), 7.83 (d, 1H, J = 8.6 Hz), 8.01 (s, 1H).

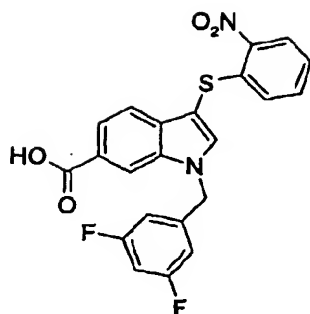
(c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (Compound 31, Structure 3 of Scheme I, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁵=CO₂Me)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indole-6-carboxylic acid methyl ester (330 mg, 1.10 mmol) in dichloromethane (30 mL) was added at room temperature a solution of 2-nitrobenzenesulfenyl chloride (210 mg, 1.11 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated and the crude product was purified over a 20 g silica SPE cartridge (ethyl acetate/heptane 1:5 to 1:2) to give the title compound as a yellow solid (392 mg, yield = 78%).

HPLC: 4.60 min (97.8%); ¹H NMR (CDCl₃): δ 3.93 (s, 3H, CO₂CH₃), 5.45 (s, 2H, NCH₂Ar), 6.63-6.69 (m, 2H), 6.74-6.80 (m, 1H), 6.88 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.2 Hz), 7.18-7.23 (m, 1H), 7.26-7.30 (m, 1H), 7.57 (d, 1H, J = 7.8 Hz), 7.58 (s, 1H), 7.89 (dd, 1H, J₁ = 7.8 Hz, J₂ = 1.2 Hz), 8.12 (s, 1H), 8.28 (dd, 1H, J₁ = 7.8 Hz, J₂ = 1.2 Hz).

Example 3

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid (Compound 30, Structure 14 of Scheme IV, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H)

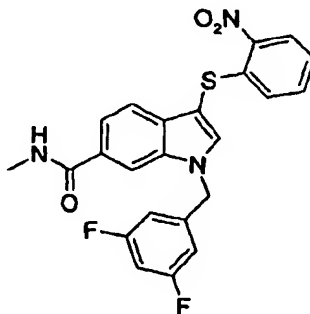


To a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methyl ester (150.0 mg, 0.33 mmol) in dioxane (20 mL) and water (15 mL) was added LiOH.H₂O (83.1 mg, 2.0 mmol) in 5 ml water. The reaction mixture was stirred overnight at 60°C. The mixture was then acidified to pH 4 by addition of 15% aqueous HCl and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as yellow/orange crystals (129.3 mg, *y* = 89%)

¹H NMR (DMSO): δ 5.62 (s, 2H, CH₂Ar), 6.85 (dd, 1H, J₁ = 8.6 Hz, J₂ = br), 7.05 (m, 2H, br), 7.20 (m, 1H, br), 7.32-7.38 (m, 1H), 7.40 (d, 1H, J = 8.2 Hz), 7.44-7.50 (m, 1H), 7.68 (dd, 1H, J₁ = 8.6 Hz, J₂ = br), 7.97 (s, 1H, COOH), 8.20 (s, 1H), 8.26 (s, 1H), 8.28 (d, 1H, J = 8.2)

Example 4

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid methylamide (Compound 47, Structure 15 of Scheme IV, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=R⁸=H, R⁹=Me)



General method 2: amidation of 6-carboxyl indoles of structure **14** to give 6-carboxamideindoles of structure **15** (Scheme IV).

- 5 Under nitrogen atmosphere: to a solution of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid (25.1 mg, 57.0 μmol) in dry DMF (10mL) was added NMM (1 mL), HOBT (9.60 mg, 62.7 μmol), EDCI (12.1 mg, 62.7 μmol), and methylammonium chloride (19.2 mg, 285 μmol). The reaction mixture was stirred overnight at room temperature and then poured into ice water. The resulting precipitate was filtered and the residue was washed with excess water followed by little heptane.
- 10 The product was dried *in vacuo* at 40°C to give the title compound as a yellow solid (15.2 mg, $y = 60\%$).

- LCMS: 4.31 min (100.0%, $\text{MH}^+ = 454$); ^1H NMR (DMSO): δ 2.80(d, 3H, $J = 4.3$, CH_3NHCO), 5.63 (s, 2H, CH_2Ar), 6.86 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 7.04 (m, 2H), 7.20 (m, 1H), 7.33-7.37 (m, 1H), 7.41 (d, 1H, 8.6 Hz), 7.46-7.50 (m, 1H), 7.64 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 8.15 (s, 1H), 8.25 (s, 1H), 8.27 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 1.0$ Hz), 8.40 (m, 1H, MeNHCO).
- 15

According to General method 2 the following compounds were prepared:

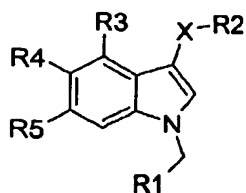


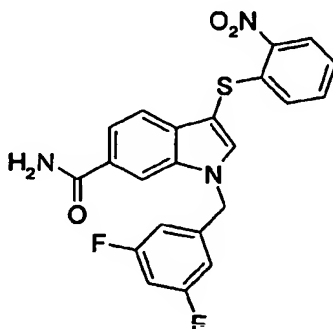
Table 2 Compounds synthesised according to General Method 2

								LCMS	LCMS
									ret.
Compound									Time ^a
number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt	(MH ⁺)	(min)
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	493.53	494	4.66
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	509.53	510	4.50
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4-methylpiperazinyl)]	522.57	523	3.81
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONEt ₂	495.55	496	4.82
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (2-furanyl)	519.53	520	4.74
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (3-pyridyl)	530.55	531	3.94
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ NMe ₂	510.56	511	3.90
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OH	483.49	484	4.21
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OMe	497.52	498	4.48
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CO ₂ Me	511.50	512	4.51
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CONMe ₂	524.55	525	4.33
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ cPr	493.53	494	4.75
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ iPr	495.55	496	4.85
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ Ph	529.56	530	4.90
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	479.50	480	4.57
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHEt	467.49	468	4.56
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	481.52	482	4.71
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	453.47	454	4.31
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	481.52	482	4.75
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe ₂	467.49	468	4.30 ^b

a) 7 min LCMS method was used, unless stated otherwise. b) 10 min LCMS method was used.

Example 5

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (Compound 33, Structure 16 of Scheme IV, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$)



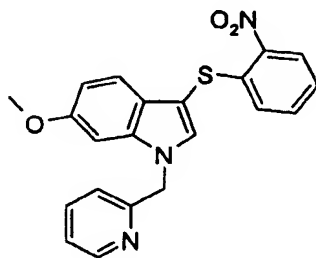
5

The title compound was prepared according to General method 2, using 51.1 mg (116 μ mol) carboxylic acid, 19.5 mg (128 μ mol) HOBt, 24.6 mg (128 μ mol) EDCI and 31.1 mg (581 μ mol) ammonium chloride. The title compound was obtained as a yellow solid (9.0 mg; 18%).

- 10 LCMS: 4.16 min (100.0%, $MH^+ = 440$); 1H NMR ($CDCl_3$): δ 5.46 (s, 2H, CH_2Ar), 6.65 (m, 2H), 6.77 (m, 1H), 6.88 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz), 7.21 (m, 1H), 7.29 (m, 1H), 7.51 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.0$ Hz), 7.57 (d, 1H, $J = 7.7$ Hz), 7.58 (s, 1H), 8.05 (s, 1H), 8.29 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz).

15 **Example 6**

6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound 9, Structure 3 of Scheme I, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$)



20

General method 3: 3-sulfanylation of a (un)substituted indole of structure 1 to give substituted indoles of structure 4, followed by indole-*N*-alkylation to give *N*-alkylated indole structure 3 (Scheme I).

- 5 (a) 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (Structure 4 of Scheme I, where $R^2 = 2\text{-nitrophenyl}$, $R^1 = R^3 = R^4 = \text{H}$, $R^5 = \text{OMe}$)

To a solution of 6-methoxyindole (1.5 g, 10.2 mmol) in Et₂O (100 mL) was added a solution of 2-nitrobenzenesulfonyl chloride (1.93 g, 10.2 mmol) in 50 mL Et₂O dropwise, over a 4 minute period. The resulting yellow solution was stirred at room temperature for 1 h. The solvent was evaporated and the crude product was purified over a silica column (heptane/ethyl acetate 9:1) to give the title compound (3.054 g, yield = 97%).

HPLC : 3.72 min. purity 96.7%, TLC (heptane/ethyl acetate 1:1): $R_f = 0.6$;

¹H NMR (CDCl₃): δ 3.87 (s, 3H, OCH₃), 6.84 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 3.13$ Hz), 6.97 (m, 2H), 7.16 (t, 1H, $J = 7.8$ Hz), 7.25 (t, 1H, $J = 7.8$ Hz), 7.36 (d, 1H, $J = 7.8$ Hz), 7.44 (d, 1H, $J = 2.0$ Hz), 8.26 (d, 1H, $J = 7.8$ Hz), 8.45 (s, 1H, NH).

- (b) 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole (Compound 9, Structure 3 of Scheme I, where $R^1 = 2\text{-pyridyl}$, $R^2 = 2\text{-nitrophenyl}$, $R^3 = R^4 = \text{H}$, $R^5 = \text{OMe}$)

20 To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (1.5 g, 5 mmol) in DMF (150 mL) was added NaH (60% in oil; 500 mg, 12.5 mmol) in small portions, over a 4 minute period. The resulting dark solution was stirred for 5 min. at room temperature. Then 2-picolyl chloride hydrochloride (984 mg, 6 mmol) was added in small portions, over a 2 minute period. During stirring at room temperature (2h) the colour of the solution slightly changed from dark to yellow. Ethyl acetate (100 mL) was added and the mixture was washed with 2% aqueous citric acid (2x100 mL) and water (100 mL). The organic phase was dried (MgSO₄) and the solvent was evaporated. The crude product was purified by crystallisation (ethyl acetate/heptane) to give the title compound (1.437 g, yield = 74%).

30 HPLC : 10.3 min, purity 99.6%, TLC (heptane/ethyl acetate 1:1): $R_f = 0.3$;

¹H NMR (CDCl₃): δ 3.80 (s, 3H, OCH₃), 5.47 (s, 2H, NCH₂), 6.82 (m, 2H), 6.88 (d, 1H, $J = 7.8$ Hz), 7.01 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 7.15-7.19 (m, 1H), 7.25 (m,

2H), 7.37 (d, 1H, $j = 8.6$ Hz), 7.60-7.64 (m, 1H), 8.26 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 8.63 (d, 1H, $J = 5.88$ Hz).

According to General method 3 the following compounds were prepared:

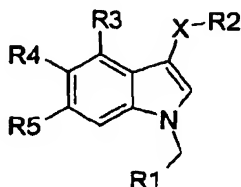


Table 3 Compounds synthesised according to General Method 3

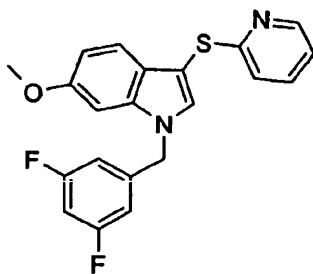
Compound number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt	LCMS	LCMS ret.
								(MH ⁺)	Time ^a (min)
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	426.44	427	4.07
2	S	2,fluoro,3-methylphenyl	2-nitrophenyl	H	H	OMe	422.48	423	4.23
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.17
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.97
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.10
6	S	2-methyl,3-nitrophenyl	2-nitrophenyl	H	H	OMe	449.48	450	4.10
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.16
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	436	4.08
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	391.45		10.30 ^b
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	398.48	399	4.68
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	459	4.29
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	395.44	396	4.66
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	459	4.33
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	459.35	459	4.36
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.34
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.92
69	S	3-fluoro,5-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	477	4.42
70	S	3-fluoro,6-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	476.45	477	4.27
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.22

Compound								LCMS	LCMS ret.
number	X	R ¹	R ²	R ³	R ⁴	R ⁵	MWt	(MH ⁺)	Time ^a (min)
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	421	4.04
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.16
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	435.46	436	4.00
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	391.45	392	3.28
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	492.90	493	4.33
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	474.46	475	4.43
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	458.46	459	4.21
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	411.50	412	4.39
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	409.46	410	4.49
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	424.91	425	4.22
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	415.47	416	3.93
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	408.45	409	4.07
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	420.49	421	4.03
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	404.49	405	4.19
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	413.50	414	3.54
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	431.92	432	4.61
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	430.93	431	4.92
89	S	cyclohexyl	2-nitrophenyl	H	H	OMe	396.51	397	5.11

a) 7 min LCMS method was used unless stated otherwise. b) a 20 min run on an HPLC system was used.

Example 7

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(pyridin-2-ylsulfanyl)-1H-indole (Compound 65 , Structure 3 of Scheme I, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -pyridyl, $R^3=R^4=H$, $R^5=OMe$)



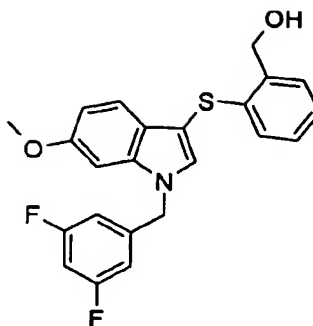
Under a nitrogen atmosphere: to a cooled (-10°C) solution of 2-mercaptopyridine (25 mg, 0.22 mmol) in CCl_4 (2 mL) was passed Cl_2 -gas during a period of 1 minute. The solvent was evaporated and a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indole (25 mg, 0.09 mmol) in Et_2O (2 mL) was added dropwise. The reaction mixture was concentrated and the crude product was purified by preparative LCMS to give the title compound (7.77 mg, yield = 23%).

LCMS : 3.95 min (100%, MH^+ 383); TLC (heptane/ethyl acetate 1:1): $R_f = 0.6$;

$^1\text{H-NMR}$ (CDCl_3) : δ 2.23 (s, 1H, NH), 3.82 (s, 1H, OCH_3), 6.65 (m, 2H), 6.73 (d, 1H, $J = 2.7$ Hz), 6.73-6.78 (m, 1H), 6.80 (d, 1H, $J = 7.8$ Hz), 6.87 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 7.00 (ddd, 1H, $J_1 = 9.8$ Hz, $J_2 = 4.7$ Hz, $J_3 = 0.8$ Hz), 7.35 (s, 1H), 7.42 (ddd, 1H, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.6$ Hz), 7.50 (d, 1H, 8.6 Hz), 8.46 (d, 1H, $J = 4.7$ Hz).

Example 8

{2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1H-indol-3-ylsulfanyl]-phenyl}-methanol (Compound 16 , Structure 8 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)



- 5 a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (Compound 19, Structure 7 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

Chlorine gas was bubbled through CCl_4 (5 mL) at $-10^\circ C$ for 3 min. Then a solution of methylthiosalicylate (91 μL , 0.66 mmol) in CCl_4 (2 mL) was added. The mixture was stirred at $-10^\circ C$ for 5 min and then at room temperature for 15 min. The mixture was concentrated and redissolved in CH_2Cl_2 (5 mL). To this solution a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indole (121 mg, 0.443 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at room temperature for 2 h and was concentrated. The crude product was purified by column chromatography (ethyl acetate/heptane 1:9) to give the title compound as a white solid (161 mg, 83% yield). LCMS: 4.72 min ($MH^+ = 440$); 1H -NMR ($CDCl_3$): δ 3.82 (s, 3H, $ArOCH_3$), 3.99 (s, 3H, CO_2CH_3), 5.30 (s, 2H, CH_2Ar), 6.62-6.69 (m, 2H), 6.71-6.77 (m, 2H), 6.83 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 2.4$ Hz), 6.87 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz), 7.06-7.11 (m, 1H, 7.15-7.20 (m, 1H), 7.30 (s, 1H), 7.44 (d, 1H, $J = 8.6$ Hz), 8.02 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz).

- 20 b) {2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-phenyl}-methanol (Compound 16, Structure 8 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

Under a nitrogen atmosphere: to a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (13.5 mg, 0.031 mmol) in THF (2 mL) was added $LiAlH_4$ (1.0 M in THF, 0.040 mL, 0.040 mmol). The mixture was stirred at room temperature for 3 h. Then ethyl acetate (25 mL) was added and the mixture was washed with 3% aqueous citric acid (2x25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a colourless oil (15 mg). The crude product

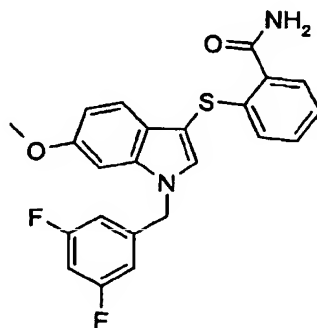
was purified by prep. HPLC to give the title compound as a colourless oil (5.6 mg, 44% yield).

LCMS: 4.47 min (95.6%, $MH^+ = 412$); 1H -NMR ($CDCl_3$) : δ 3.49 (s, 1H, OH), 3.81 (3, 3H, OCH_3), 4.92 (s, 2H, CH_2OH), 5.28 (s, 2H, CH_2Ar), 6.62-6.66 (m, 2H), 6.70-6.77 (m, 2H), 6.83 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz), 6.89 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz), 7.02-7.07 (m, 1H), 7.08-7.13 (m, 1H), 7.29 (s, 1H), 7.38 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz), 7.44 (d, 1H, $J = 8.8$ Hz).

Example 9

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (Compound 18, Structure 11 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

5



a) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (Structure 9 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

10 To a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid methyl ester (97 mg, 0.221 mmol) in THF (10 mL) was added a solution of LiOH·H₂O (71 mg, 1.69 mmol) in water (10 mL). The mixture was stirred at room temperature for 17 h and then at 60°C for 24 h and was then acidified with 3% aqueous citric acid. Ethyl acetate (50 mL) was added and the mixture was washed with 3%
15 aqueous citric acid (2x50 mL) and brine (50 mL). The organic phase was dried (MgSO₄) and concentrated to give a yellow solid (104 mg). The crude product was recrystallised from ethyl acetate/heptane to give the title compound as a yellow powder (49 mg, 52% yield).

LCMS: 4.37 min (MH⁺ = 426); ¹H-NMR (CDCl₃) : δ 3.77 (s, 3H, OCH₃), 5.51 (s, 2H, CH₂Ar), 6.69 (d, 1H, J = 8.0 Hz), 6.76 (dd, 1H, J₁ = 8.4 Hz, J₂ = 2.4 Hz), 6.98-7.04 (m, 2H), 7.11-7.15 (m, 1H), 7.16-7.25 (m, 4H), 7.83 (s, 1H), 7.92 (dd, 1H, J₁ = 8.0 Hz, J₂ = 1.6 Hz).

General method 4: Reaction of an amine with a carboxylic acid of structure 9, with
25 TBTU and DIPEA, to give amides of structure 3, in which $R^2 =$ phenyl-2-carboxamide, exemplified by compounds of structure 10 and 11 (Scheme III).

b) 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide

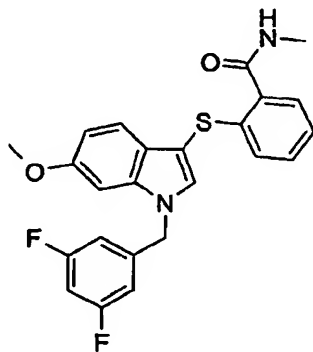
(Compound 18, Structure 11 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

Through a solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzoic acid (36 mg, 0.085 mmol), TBTU (28 mg, 0.087 mmol) and DIPEA (30 μ L, 0.172 mmol) in DMF (1 mL) was bubbled NH_3 gas for 10 min. The mixture was then stirred at room temperature for 3 days. Then 3% aqueous citric acid (0.4 mL) was added and the crude reaction mixture was purified over a RP-SPE cartridge (2g sorbent; 25% aqueous methanol to 100% methanol) to give a white solid (34 mg). The crude product was purified by column chromatography (ethyl acetate) to give the title compound as a colourless oil, which solidifies on standing (31 mg, yield: 86%).

LCMS: 4.20 min ($MH^+ = 425$); 1H -NMR ($CDCl_3$): δ 3.81 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2Ar), 6.05 (s, br, 1H, NH), 6.28 (s, br, 1H, NH), 6.61-6.67 (m, 2H), 6.70-6.72 (m, 1H), 6.73-6.77 (m, 1H), 6.83 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 2.0$ Hz), 6.92 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz), 7.07-7.17 (m, 2H), 7.31 (s, 1H), 7.45 (d, 1H, $J = 8.8$ Hz), 7.60 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz).

Example 10**2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-*N*-methyl-benzamide**

(Compound 17, Structure 10 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)



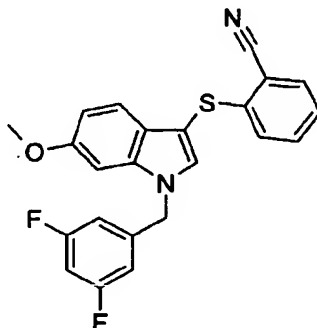
According to general method 4 compound 17 was synthesised from methylamine.

LCMS: 4.07 min ($MH^+ = 439$).

Example 11

2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzonitrile (Compound 20, Structure 12 of Scheme III, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $R^5=OMe$)

5



To a cooled (0°C) solution of 2-[1-(3,5-Difluoro-benzyl)-6-methoxy-1*H*-indol-3-ylsulfanyl]-benzamide (8 mg, 0.019 mmol) and Et₃N (10 µL, 0.072 mmol) in CH₂Cl₂ (1.5 mL) was added Tf₂O (6 µL, 0.036 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 22 h. Water (25 mL) was added and the mixture was extracted with CH₂Cl₂ (2x25 mL). The combined organic phases were dried (Na₂SO₄) and concentrated to give a brown oil (25 mg). The crude product was purified by column chromatography (ethyl acetate/heptane 1:2) to give the title compound as a pale pink oil (3 mg, yield: 39%).

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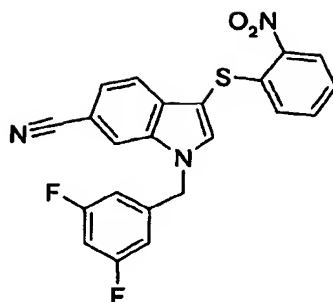
LCMS: 4.57 min (MH⁺ = 407); ¹H-NMR (CDCl₃): δ 3.82 (s, 3H, OCH₃), 5.30 (s, 2H, CH₂Ar), 6.62-6.67 (m, 2H), 6.71-6.73 (m, 1H), 6.74-6.78 (m, 1H), 6.86 (dd, 1H, J₁ = 8.8 Hz, J₂ = 2.0 Hz), 6.91 (d, 1H, J = 8.4 Hz), 7.11-7.15 (m, 1H), 7.26-7.30 (m, 1H), 7.37 (s, 1H), 7.46 (d, 1H, J = 8.8 Hz), 7.57-7.60 (m, 1H).

20

Example 12

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile (Compound 26, Structure 17 of Scheme IV, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$)

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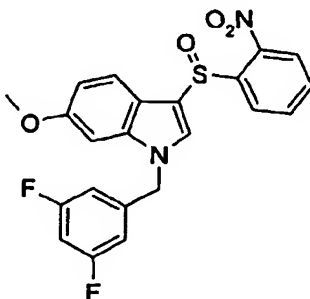


To a cooled (0°C) suspension of 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carboxylic acid amide (15 mg, 0.034 mmol) and Et₃N (10 µL, 0.072 mmol) in CH₂Cl₂ (1.5 mL) was added Tf₂O (13 µL, 0.077 mmol). The mixture was stirred at 0°C for 2 h and then at room temperature for 20 h. Water (25 mL) was added and the mixture was extracted with CH₂Cl₂ (2x25 mL). The combined organic phases were dried (Na₂SO₄) and concentrated to give the title compound as a yellow solid (13 mg, yield: 91%).

LCMS: 4.55 min (MH⁺ = not detectable); ¹H-NMR (CDCl₃): δ 5.42 (s, 2H, CH₂Ar), 6.63-6.69 (m, 2H), 6.78-6.85 (m, 2H), 7.21-7.25 (m, 1H), 7.28-7.33 (m, 1H), 7.44 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.2 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), 8.29 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.6 Hz).

Example 13

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfinyl)-1*H*-indole (Compound 64, Structure 5 of Scheme II, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁵=OMe)



20

To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (40 mg, 0.09 mmol) in CH₂Cl₂ (4 mL) was added meta-chloroperbenzoic acid (14.5, 0.08 mmol). The solution was stirred at room temperature for 2 h. The solvent

was evaporated and the crude product was purified by prep LC-MS to give the title compound (14.3 mg, yield = 34%).

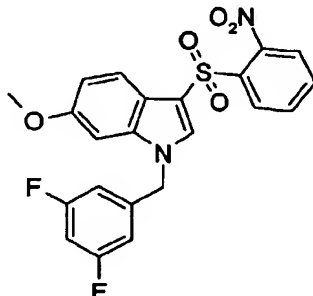
HPLC : 4.13 min, purity 100%; TLC (heptane/ethyl acetate 1:1) : R_f = 0.4; ^1H NMR (CDCl_3): δ 3.66 (s, 3H, OCH_3), 5.12 (s, 2H), 6.57 (m, 3H), 6.75 (m, 2H), 7.47 (d, 1H, J = 7.8 Hz), 7.52 (s, 1H), 7.66-7.70 (m, 1H), 8.28-8.32 (m, 1H), 8.23 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.9 Hz), 8.80 (dd, 1H, J_1 = 7.8 Hz, J_2 = 3.1 Hz).

5

Example 14

1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-benzenesulfonyl)-1*H*-indole (Compound 62, Structure 6 of Scheme II, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$)

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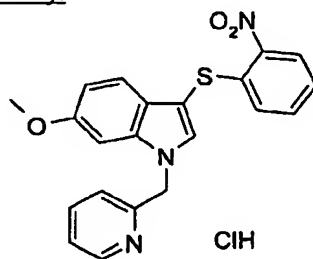
To a solution of 1-(3,5-Difluoro-benzyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole (40 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) was added meta-chloroperbenzoic acid (46.5 mg, 0.27 mmol). The solution was stirred at room temperature for 6 h. The solvent was evaporated and the crude product was purified by LC-MS to give the title compound (14.5 mg, yield = 34%).

HPLC: 4.38 min. purity 100%; TLC (heptane/ethyl acetate 1:1) : $R_f = 0.6$; 1H NMR ($CDCl_3$): δ 3.71 (s, 3H, OCH_3), 5.25 (s, 2H), 6.58 (d, 1H, $J = 3.1$), 6.62 (m, 1H), 6.07-6.11 (m, 1H), 6.88 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 3.1$ Hz), 7.63 (m, 4H), 7.72 (d, 1H, $J = 7.8$ Hz), 7.83 (s, 1H), 8.37 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.9$ Hz).

Example 15

6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole monohydrochloride (Compound 10).

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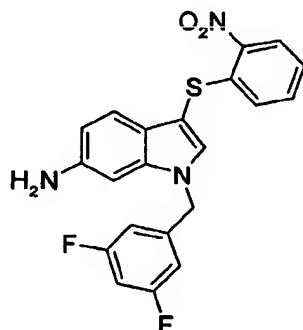
To a solution of 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole in methylene chloride was passed HCl-gas till the organic salt crystallised. The title compound was isolated by filtration.

25

LC-MS : 4.04 min ($MH^+ = 392$); 1H NMR (DMSO): δ 3.78 (s, 3H, OCH₃), 5.78 (s, 2H, NCH₂), 6.77 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 2.0$ Hz), 6.93 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 0.8$ Hz), 7.22 (d, 1H, $J = 7.8$ Hz), 7.26 (d, 1H, $J = 2.0$ Hz), 7.34 (m, 2H), 7.48-7.52 (m, 1H), 7.59 (t, 1H, $J = 7.0$ Hz), 7.96 (s, 1H), 8.08 (t, 1H, $J = 7.0$ Hz), 8.27 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 8.74 (d, 1H, $J = 6.7$ Hz).

Example 16

1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (Compound 57, Structure 23 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$)



a) 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole (Structure 19 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^3 = R^4 = H$)

To a solution of 6-nitroindole (162 mg, 1.0 mmol) in DMF (4 mL) was added NaH (60% dispersion on oil; 80 mg, 2.0 mmol). The resulting dark solution was stirred at room temperature for 15 minutes. 3,5-difluorobenzyl bromide (129 μ L, 1.1 mmol) was added. The reaction mixture was stirred overnight, poured into acidified water and extracted twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*.

The product was purified over a SiO₂ column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (270 mg, yield = 94%).

LCMS: 5.54 min (100.0%, $MH^+ = 289$); 1H NMR (CDCl₃): δ 5.40 (s, 2H, CH₂Ar), 6.58 (m, 2H), 6.71 (d, 1H, $J = 3.5$ Hz), 6.75 (m, 1H), 7.26 (s, 1H), 7.41 (d, 1H, $J = 3.5$ Hz), 7.71 (d, 1H, $J = 8.3$ Hz), 8.05 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz), 8.21 (d, 1H, $J = 2.0$ Hz).

b) 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (Structure 20 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^3 = R^4 = H$)

To a solution of 1-(3,5-Difluoro-benzyl)-6-nitro-1*H*-indole (144 mg, 0.5 mmol) in ethanol (20 mL) was added hydrochloric acid 37% (80 μ L) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (600 mg). The reaction mixture was stirred at 60 °C for 40 h and was then concentrated *in vacuo*. The residue was poured into ethyl acetate and a concentrated NaHCO_3 -solution was added. The two-layer phase system was filtered over decalite to get rid of the tin salts and the filtrate was twice extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as a colourless oil (89 mg, yield = 69%).

LCMS: 3.20 min (97.7%, $\text{MH}^+ = 259$); ^1H NMR (CDCl_3): δ 5.12 (s, 2H, CH_2Ar), 6.52 (m, 2H), 6.56 (d, 1H, $J = 3.5$ Hz), 6.63 (m, 1H), 7.97 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz), 7.13 (d, 1H, $J = 3.5$ Hz), 7.17 (d, 1H, $J = 2.0$ Hz), 7.55 (d, 1H, $J = 8.3$ Hz).

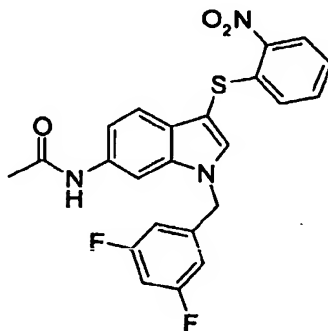
c) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (Compound 57, Structure 23 of Scheme V, where $\text{R}^1 = 3,5$ -difluorophenyl, $\text{R}^2 = 2$ -nitrophenyl, $\text{R}^3 = \text{R}^4 = \text{H}$)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added 2-nitrobenzenesulfenyl chloride. The resulting yellow solution was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and purified over a SiO_2 column (heptane/ethyl acetate 9:1) to give the title compound as an orange solid (11.6 mg, yield = 28%).

LCMS: 5.11 min (100.0%, $\text{MH}^+ = 412$); ^1H NMR (CDCl_3): δ 5.22 (s, 2H, CH_2Ar), 6.56 (m, 2H), 6.65 (m, 1H), 6.84 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz), 7.00 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz), 7.19 (m, 1H), 7.30 (d, 1H, $J = 1.2$ Hz), 7.31 (s, 1H), 7.37 (d, 1H, $J = 8.2$ Hz), 7.49 (m, 1H), 8.27 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz).

Example 17

N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide
 (Compound 58, Structure 22 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z = \text{methyl}$)



General method 5: Reaction of an acid anhydride with a 6-aminoindole of structure 20 to give compounds of structure 21, followed by sulfanylation of the indole 3-position to give compounds of structure 22 (Scheme V).

a) *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-acetamide (Structure 21 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^3=R^4=H$, $Z = \text{methyl}$)

To a solution of 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (25 mg, 0.1 mmol) in DCM (4 mL) was added pyridine (25 μL) and acetic anhydride (9.8 μL , 0.11 mmol) and stirred overnight at room temperature. The reaction mixture was poured into 10 mL of water and neutralised with NaHCO_3 and extracted twice with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude compound as a off white solid (23.3 mg, yield = 84%). The product was used without further purification.

LCMS: 4.10 min (97.4%, $\text{MH}^+ = 301$); ^1H NMR (CDCl_3): δ 2.18 (s, 3H, CH_3CON), 5.28 (s, 2H, CH_2Ar), 6.53 (d, 1H, $J = 3.1$), 6.58 (m, 2H), 6.68 (m, 1H), 6.87 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz), 7.07 (d, 1H, $J = 3.1$ Hz), 7.55 (d, 1H, $J = 8.3$ Hz), 7.90 (s, 1H).

b) *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-acetamide
 (Compound 58, Structure 22 of Scheme V, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z = \text{methyl}$)

To a solution of *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-acetamide (23.3 mg, 0.08 mmol) in diethyl ether (4 mL) was added 2-nitrobenzenesulfenyl chloride (14.7 mg,

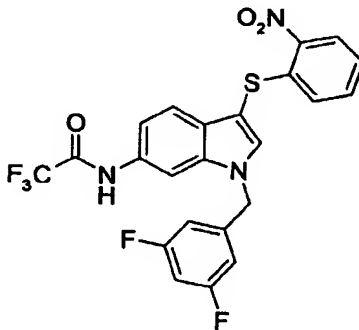
0.09 mmol). The resulting yellow solution was stirred overnight at room temperature.

The mixture was concentrated *in vacuo* and purified over a SiO₂ column (heptane/ethyl acetate 9:1) to give the title compound as a yellow solid (35.0 mg, yield = 96%).

LCMS: 4.26 min (98.6%, MH⁺ = 454); ¹H NMR (DMSO): δ 2.03 (s, 3H, CH₃CON), 5.51 (s, 2H, CH₂Ar), 6.89 (dd, 1H, J = 8.3 Hz, J2 = 1.2 Hz), 6.95 (m, 2H), 7.17 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.19 (m, 1H), 7.27 (d, 1H, J = 8.3 Hz), 7.34 (m, 1H), 7.49 (m, 1H), 7.97 (d, 1H, J = 1.2 Hz), 8.02 (s, 1H), 8.27 (dd, 1H, J1 = 8.3 Hz, J2 = 1.2 Hz).

Example 18

N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (Compound 59, Structure 22 of Scheme V, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, Z = trifluoromethyl)



According to General method 5, step a): *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using 1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine (17.7 mg, 69 μmol), pyridine (17 μL) and trifluoroacetic anhydride (9.68 μL, 70 μmol). The compound was purified over a SiO₂ column (heptane/ethyl acetate 9:1) to give the title compound as a white solid (10.9 mg, yield = 61%).

LCMS: 4.41 min (82.1%, MH⁺ = 355)

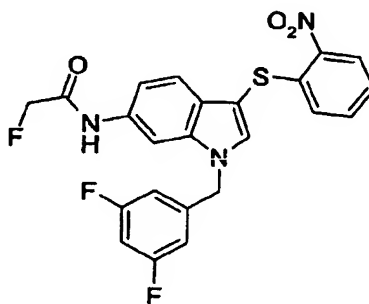
According to General method 5, step b): *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide was prepared using *N*-[1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-2,2,2-trifluoro-acetamide (10.9 mg, 31 μmol) and 2-nitrobenzenesulfonyl chloride (5.7 mg, 37 μmol). The compound was purified over an HPLC column (MeCN/H₂O) to give the title compound as a yellow solid (10.2 mg, yield = 65%).

LCMS: 4.65 min (89.0%, MH⁺ = 508); ¹H NMR (DMSO): δ 5.56 (s, 2H, CH₂Ar), 6.87 (dd, 1H, J = 8.3 Hz, J2 = 1.2 Hz), 7.01 (m, 2H), 7.20 (m, 1H), 7.35 (m, 1H), 7.37 (dd,

1H, J1 = 8.3 Hz, J2 = 2.0 Hz), 7.39 (d, 1H, J = 8.3 Hz), 7.49 (m, 1H), 7.50 (d, 1H, J = 2.0 Hz), 8.15 (s, 1H), 8.28 (dd, 1H, J1 = 8.3 Hz, J2 = 2.0 Hz).

Example 19

- 5 Compound 97: N-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1H-indol-6-yl]-2-fluoro-acetamide, structure 28 of Scheme VII, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, Z¹= monofluoromethyl.



- 10 a) 1-(3,5-Difluoro-benzyl)-6-nitro-1H-indole, structure 19 of Scheme VII, where R¹ = 3,5-difluorophenyl, R²=R³=R⁴=H.

To a solution of 6-nitro-1H-indole (19.5 g, 120 mmol) in NMP (500 mL) was added at 0 °C cesium carbonate (39.1 g, 120 mmol). After stirring for 30 min at 0 °C 3,5-difluorobenzyl bromide (30.0 g, 144 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 18 hrs. The mixture was poured into saturated aqueous ammonium chloride (1 L) and extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with H₂O (2 x 500 mL) and brine (500 mL) and dried (Na₂SO₄) and concentrated to give the title compound (65 g, yellow solid) which was used without further purification.

- 15 b) 1-(3,5-Difluoro-benzyl)-1H-indol-6-ylamine, structure 20 of Scheme VII, where R¹ = 3,5-difluorophenyl, R²=R³=R⁴=H.

EtOH 96% (1L) was added to 1-(3,5-difluoro-benzyl)-6-nitro-1H-indole and the mixture was stirred at 60 °C until all material was dissolved. 37% HCl (37 mL) was added followed by tin(II)chloride dihydrate (268 g, 1.19 mol) and stirring was continued at 60 °C for 18 hrs. After the mixture was cooled to room temperature the solvent was removed under reduced pressure. Ethyl acetate (800 mL) was added and the mixture was poured into saturated aqueous NaHCO₃ (1 L) and filtered over kieselguhr. The layers were separated and the organic layer was washed with H₂O (2 x 500 mL) and

brine (500 mL), dried (Na_2SO_4) and concentrated to afford the the title compound (54 g, brown oil/solid) which was used without further purification.

c) [1-(3,5-Difluoro-benzyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester, structure 26 of Scheme VII, where $\text{R}^1 = 3,5\text{-difluorophenyl}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$.

1-(3,5-Difluoro-benzyl)-1*H*-indol-6-ylamine was dissolved in NMP (1 L) and triethylamine (34 mL, 242 mmol) was added followed by di-*tert*-butyl dicarbonate (53 g, 242 mmol) and the mixture was stirred at room temperature for 18 hrs. The mixture was poured into saturated aqueous NaHCO_3 (1.5 L) and extracted with ethyl acetate (3 x 750 mL). The combined organic layers were washed with H_2O (1 L) and brine (1 L), dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography (heptane/ethyl acetate 4:1) to afford the title compound (39 g, 109 mmol, 91% (three steps), white solid).

d) [1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester, structure 27 of Scheme VII, where $\text{R}^1 = 3,5\text{-difluorophenyl}$, $\text{R}^2 = 2\text{-nitrophenyl}$, $\text{R}^3 = \text{R}^4 = \text{H}$.

To a solution of [1-(3,5-difluoro-benzyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester (39 g, 109 mmol) in diethylether (750 mL) was added 2-nitrobenzenesulfenyl chloride (20.4 g, 109 mmol) and the reaction mixture was stirred at room temperature for 18 hrs. The mixture was poured into saturated aqueous NaHCO_3 (1 L) and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were washed with H_2O (400 mL) and brine (400 mL), dried and concentrated to afford the title compound (56 g, yellow solid) which was used without further purification.

e) 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine, structure 23 of Scheme VII, where $\text{R}^1 = 3,5\text{-difluorophenyl}$, $\text{R}^2 = 2\text{-nitrophenyl}$, $\text{R}^3 = \text{R}^4 = \text{H}$.

[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-carbamic acid *tert*-butyl ester was dissolved in CH_2Cl_2 (1 L) and under nitrogen atmosphere trifluoroacetic acid (48 mL, 624 mmol) was added dropwise at room temperature. After stirring for 1 h another portion of trifluoroacetic acid (48 mL, 624 mmol) was added and the reaction mixture was stirred for an additional hour. The mixture was diluted with CH_2Cl_2 (500 mL) and H_2O (1 L) and 3N NaOH solution was added until the pH of the mixture was 11-12. The layers were separated and the organic layer was washed with H_2O (500 mL) and brine (500 mL), dried (Na_2SO_4) and concentrated to afford the crude product. The

product was purified using column chromatography (heptane/ethylacetate 1:1) to give the title compound (28 g, 68 mmol, 63 % (two steps), red/brown solid).

General method 6: Reaction of an acid chloride (method a), carboxylic acid (method b) or sulfonyl chloride (method c) with a 6-aminoindole of structure **23** to give compounds of structure **28** and **29** (Scheme VII).

Method a, b and c can all be carried out using the same procedure which is exemplified below for method a.

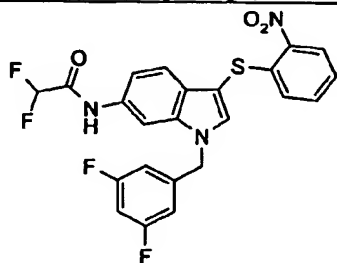
- 10 To a solution of 1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ylamine (300 mg, 0.73 mmol) in CH₂Cl₂ (7 mL) was added at 0 °C triethylamine (0.12 mL, 0.87 mmol). Subsequently monofluoroacetyl chloride (50 µL, 0.73 mmol) was added and the mixture was stirred at room temperature for 18 hrs. The mixture was concentrated and purified using flash column chromatography (CH₂Cl₂/MeOH 99:1) to afford compound
- 15 **97** (317 mg, 0.67 mmol, 92%, yellow solid).

¹H NMR (DMSO) δ 4.82 (s, 1H), 5.03 (s, 1H), 5.52 (s, 2H), 6.89 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 6.98-7.01 (m, 2H), 7.20 (tt, 1H, J₁ = 9.5 Hz, J₂ = 3.0 Hz), 7.28-7.32 (m, 2H), 7.33-7.37 (m, 1H), 7.46-7.51 (m, 1H), 7.98 (s, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 10.15 (s, 1H).

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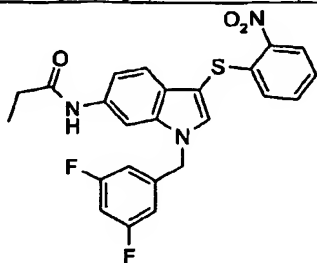
According to **general method 6** the following compounds were prepared:

Compound 98: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-2,2-difluoro-acetamide, structure **28** of Scheme VII, where R¹ = 3,5-difluorophenyl, R² = 2-nitrophenyl, R³=R⁴=H, Z¹= difluoromethyl. Method a was used.



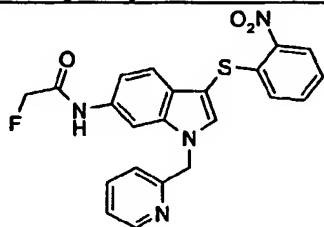
¹H-NMR (DMSO): δ 5.55 (s, 2H), 6.23-6.50 (m, 1H), 6.88 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 6.97-7.03 (m, 2H), 7.20 (tt, 1H, J₁ = 9.5 Hz, J₂ = 3.0 Hz), 7.30-7.38 (m, 3H), 7.46-7.51 (m, 1H), 7.98 (d, 1H, J = 1.1 Hz), 8.12 (s, 1H), 8.28 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 10.80 (s, 1H).

Compound 99: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-propionamide, structure 28 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{ethyl}$. Method b was used.



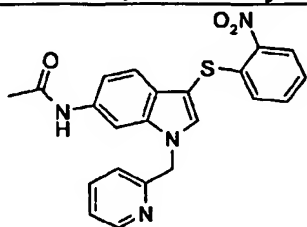
$^1\text{H-NMR}$ (DMSO): δ 1.07 (t, 3H, $J = 7.6$ Hz), 2.31 (q, 2H, $J = 7.6$ Hz), 5.51 (s, 2H), 6.89 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.93-6.97 (m, 1H), 7.16-7.23 (m, 3H), 7.27 (d, 1H, $J = 8.4$ Hz), 7.32-7.37 (m, 1H), 7.46-7.51 (m, 1H), 8.01 (d, 1H, $J = 1.1$ Hz), 8.02 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 9.92 (s, 1H).

Compound 100: 2-Fluoro-*N*-[3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{monofluoromethyl}$. Method a was used.



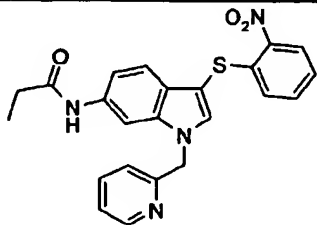
$^1\text{H-NMR}$ (CDCl_3): δ 4.88 (s, 1H), 5.00 (s, 1H), 5.51 (s, 2H), 6.94-6.99 (m, 2H), 7.06 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.18 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.22-7.29 (m, 2H), 7.46 (d, 1H, $J = 8.4$ Hz), 7.55 (s, 1H), 7.64 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 8.02 (s, 1H), 8.05 (d, 1H, $J = 2.2$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.62 (d, 1H, $J = 4.6$ Hz).

Compound 101: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{methyl}$. Method a was used.



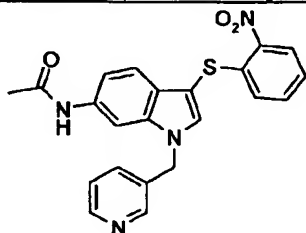
$^1\text{H-NMR}$ (CDCl_3): δ 1.80 (s, 3H), 5.48 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.30 (m, 4H), 7.40 (d, 1H, $J = 7.6$ Hz), 7.51 (s, 1H), 7.63 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.04 (d, 1H, $J = 1.5$ Hz), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.61 (d, 1H, $J = 4.6$ Hz).

Compound 102: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indol-6-yl]-propionamide, structure 28 of Scheme VII, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{ethyl}$. Method b was used.



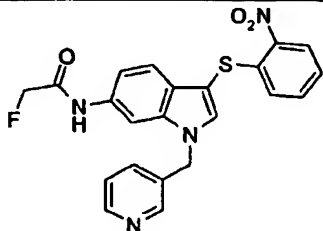
$^1\text{H-NMR}$ (CDCl_3): δ 1.25 (t, 3H, $J = 7.6$ Hz), 2.41 (q, 2H, $J = 7.6$ Hz), 5.49 (s, 2H), 6.92-6.98 (m, 3H), 7.15-7.27 (m, 4H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.51 (s, 1H), 7.63 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.12 (d, 1H, $J = 1.5$ Hz), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.61 (d, 1H, $J = 4.6$ Hz).

Compound 103: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{methyl}$. Method a was used.



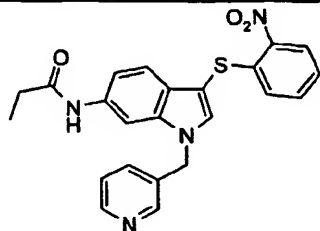
$^1\text{H NMR}$ (CDCl_3) δ 2.20 (s, 3H), 5.40 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.72 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.16-7.20 (m, 1H), 7.24-7.31 (m, 3H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.42 (s, 1H), 7.49-7.52 (m, 1H), 8.15 (d, 1H, $J = 2.2$ Hz), 8.26 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.58 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz).

Compound 104: 2-Fluoro-*N*-[3-(2-nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-acetamide, structure 28 of Scheme VII, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $Z^1 = \text{monofluoromethyl}$. Method a was used.



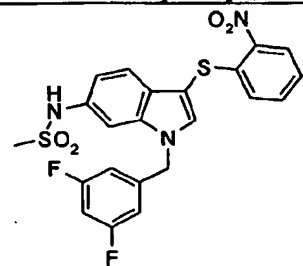
$^1\text{H NMR}$ (CDCl_3) δ 4.88 (s, 1H), 5.00 (s, 1H), 5.42 (s, 2H), 6.92 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 7.17-7.21 (m, 1H), 7.25-7.32 (m, 2H), 7.44-7.47 (d, 1H, $J = 7.6$ Hz), 7.45 (s, 1H), 7.49-7.53 (m, 1H), 8.04 (d, 1H, $J = 4.6$ Hz), 8.15 (d, 1H, $J = 1.8$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 8.56 (d, 1H, $J = 3.0$ Hz), 8.58 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.2$ Hz).

Compound 105: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indol-6-yl]-propionamide, structure 28 of Scheme VII, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^1 = \text{ethyl}$. Method b was used.



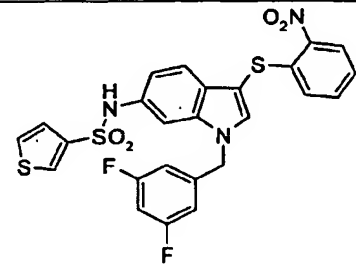
^1H NMR (CDCl_3) δ 1.26 (t, 3H, $J = 7.6$ Hz), 2.42 (q, 2H, $J = 7.6$ Hz), 5.39 (s, 2H), 8.68 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 6.91 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.15-7.20 (m, 1H), 7.24-7.30 (m, 3H), 7.38-7.41 (m, 2H), 7.48-7.52 (m, 1H), 8.23 (d, 1H, $J = 1.8$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.57 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz).

Compound 106: *N*-[1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-methanesulfonamide, structure 29 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^2 = \text{Me}$. Method c was used.



^1H -NMR (DMSO): δ 2.95 (s, 3H), 5.54 (s, 2H), 6.90 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.98-7.04 (m, 3H), 7.20 (tt, 1H, $J_1 = 9.5$ Hz, $J_2 = 3.0$ Hz), 7.31-7.37 (m, 2H), 7.41 (d, 1H, $J = 1.5$ Hz), 7.47-7.52 (m, 1H), 8.08 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 9.65 (s, 1H).

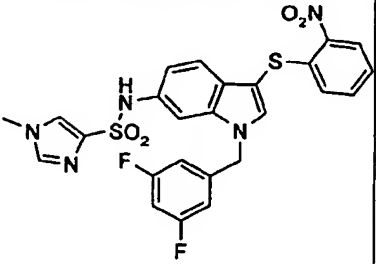
Compound 107: Thiophene-3-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-amide, structure 29 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^1 = 3$ -thiophene. Method c was used.



^1H -NMR (DMSO): δ 5.50 (s, 2H), 6.85 (m, 2H), 6.92-6.97 (m, 2H), 7.13 (dd, 1H, $J_1 = 5.0$, $J_2 = 1.1$ Hz), 7.19-7.26 (m, 2H), 7.31 (d, 1H, $J = 2.2$ Hz), 7.32-7.36 (m, 1H), 7.45-7.50 (m, 1H), 7.61 (dd, 1H, $J_1 = 5.0$ Hz, $J_2 = 3.0$ Hz), 7.97 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 1.1$ Hz), 8.05 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 10.20 (s, 1H).

Compound 108: 1-Methyl-1*H*-imidazole-4-sulfonic acid [1-(3,5-difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-yl]-amide, structure 29 of Scheme VII, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z^2 = 4$ -(1-methyl)-imidazole.

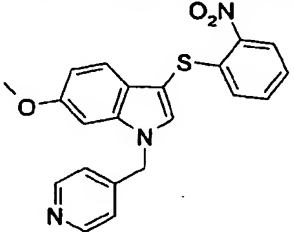
Method c was used.

	¹ H-NMR (DMSO): δ 3.60 (s, 3H), 5.46 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 0.7$ Hz), 6.92 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 6.96-7.01 (m, 2H), 7.19 (d, 1H, $J = 7.6$ Hz), 7.23 (tt, 1H, $J_1 = 9.5$ Hz, $J_2 = 3.0$ Hz), 7.31-7.36 (m, 2H), 7.45-7.49 (m, 1H), 7.66-7.69 (m, 2H), 8.02 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 0.7$ Hz), 10.20 (s, 1H).
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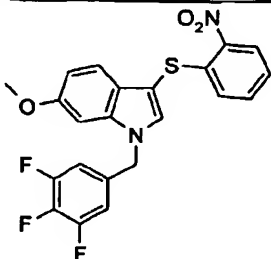
Example 20

- 5 According to general method 3 the following compounds were prepared:

Compound 93: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyridin-4-ylmethyl-1*H*-indole, structure 3 of scheme I, where $R^1 = 4$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. NaH and DMF were used.

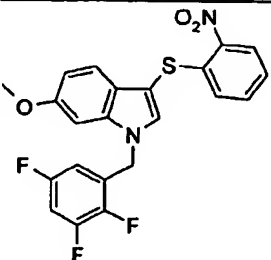
	¹ H NMR (CDCl ₃): δ 3.80 (s, 3H, OCH ₃), 5.37 (s, 2H, NCH ₂ Ar), 6.71 (d, 1H, $J = 2.7$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.7$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.04 (m, 2H), 7.19 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.29 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.36 (s, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.59 (m, 2H).
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Compound 94: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-(3,4,5-trifluoro-benzyl)-1*H*-indole, structure 3 of scheme I, where $R^1 = 3,4,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. CS_2CO_3 and NMP were used.



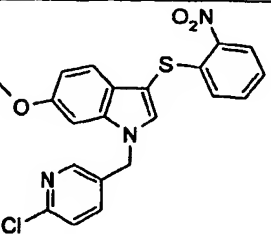
1H -NMR ($CDCl_3$): δ 3.83 (s, 3H, OCH_3), 5.28 (s, 2H, NCH_2Ar), 6.72 (d, 1H, $J = 2.2$ Hz), 6.75 (d, 1H, $J = 7.6$ Hz), 6.77 (d, 1H, $J = 7.6$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz), 6.97 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.19 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.28 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33 (s, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz).

Compound 95: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-(2,3,5-trifluoro-benzyl)-1*H*-indole, structure 3 of scheme I, where $R^1 = 2,3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. CS_2CO_3 and NMP were used.



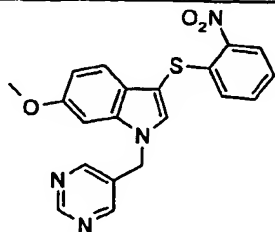
1H -NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.39 (s, 2H, NCH_2Ar), 6.42 (m, 1H), 6.82 (d, 1H, $J = 2.7$ Hz), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.90 (m, 1H), 6.96 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 7.18 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.27 (td, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.37 (s, 1H), 7.39 (d, 1H, $J = 7.6$ Hz), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz).

Compound 96: 1-(6-Chloro-pyridin-3-ylmethyl)-6-methoxy-3-(2-nitro-phenylsulfanyl)-1*H*-indole, structure 3 of Scheme I, where $R^1 = 4$ -chloro-3-pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = OMe$. CS_2CO_3 and NMP were used.



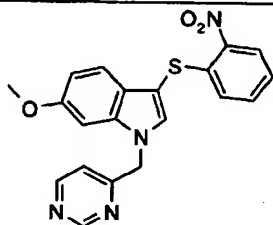
1H -NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.37 (s, 2H, NCH_2Ar), 6.76 (d, 1H, $J = 2.2$ Hz), 6.84 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 6.96 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.18 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.27 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.30-7.41 (m, 4H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.34 (d, 1H, $J = 3.0$ Hz).

Compound 115: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indole, structure 3 of Scheme I, where $R^1 = 3,5$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^5=OMe$. NaH and DMF were used. The synthesis of methanesulfonic acid pyrimidin-5-ylmethyl ester is described in example 23a).



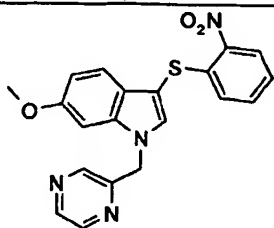
1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.38 (s, 2H), 6.77 (d, 1H, $J = 3.0$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 3.0$ Hz), 6.96 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.17-7.21 (m, 1H), 7.26-7.32 (m, 1H), 7.37 (s, 1H), 7.39 (d, 1H, $J = 8.4$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.61 (s, 2H), 9.20 (s, 1H).

Compound 116: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole, structure 3 of Scheme I, where $R^1 = 2,4$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^5=OMe$. CS_2CO_3 and NMP were used.



1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 5.44 (s, 2H), 6.74 (d, 1H, $J = 2.2$ Hz), 6.80 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 3.0$ Hz), 7.00 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.17-7.21 (m, 1H), 7.26-7.33 (m, 1H), 7.40 (d, 1H, $J = 8.4$ Hz), 7.42 (s, 1H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.66 (d, 1H, $J = 4.6$ Hz), 9.24 (d, 1H, $J = 1.1$ Hz).

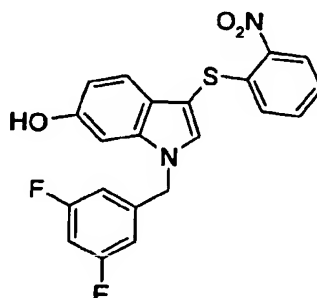
Compound 117: 6-Methoxy-3-(2-nitro-phenylsulfanyl)-1-pyrazin-2-ylmethyl-1*H*-indole, structure 3 of Scheme I, where $R^1 = 2,5$ -pyrazyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^5=OMe$. CS_2CO_3 and NMP were used.



1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 5.49 (s, 2H), 6.82-6.86 (m, 2H), 6.99 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.16-7.20 (m, 1H), 7.25-7.29 (m, 1H), 7.38 (d, 1H, $J = 8.4$ Hz), 7.46 (s, 1H), 8.26 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.35 (d, 1H, $J = 1.1$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.59-8.61 (m, 1H).

Compound 61: 1-(3,5-Difluoro-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indol-6-ol, structure 25 of Scheme VI, where $R^1 = 3,5$ -difluorophenyl, $R^2 = 2$ -nitrophenyl,

5 $R^3=R^4=H$, $R^5=OH$.

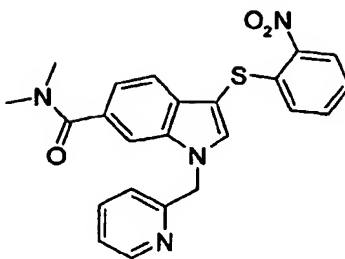


To a solution of compound **63** (240 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C boron trifluoride-methyl sulfide complex (2.37 mL, 22.5 mmol). After stirring for 2 hrs at 0 °C the reaction mixture was allowed to warm to room temperature and stirring was continued for another 4 hrs. The reaction mixture was poored into ice water (20 mL) and after addition of ethyl acetate (10 mL) the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4 . Concentration gave the crude product which was purified using flash chromatography (heptane/ethylactate 3:2) to afford compound **61** as a yellow oil (87 mg, 0.21 mmol, 38%).

1H NMR ($CDCl_3$) δ 4.75 (2, 1H), 5.29 (s, 2H), 4.66 (m, 1H), 6.72-6.79 (m, 3H), 6.98 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.17-7.21 (m, 1H), 7.27-7.31 (m, 1H), 7.35-7.37 (m, 3H), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz).

Example 22

Compound 109: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid dimethylamide, structure 15 of Scheme IV, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^8=R^9=Me$.



a) 1-Pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester.

Under a nitrogen atmosphere: to a solution of 1H-indole-6-carboxylic acid methyl ester (for synthesis see example 2a), 2.47 g, 14.1 mmol) in NMP (140 mL) was added Cs₂CO₃ (10.1 mg, 31 mmol) at 0 °C. After stirring for 15 min 2-picolyl chloride hydrochloride (2.77 g, 16.9 mmol) was added and the mixture was stirred at room temperature for 18 h. Ethyl acetate (200 mL) was added and the mixture was washed with saturated aqueous ammonium chloride (3x150 mL) and brine (200 mL). The organic phase was dried (Na₂SO₄) and concentrated. The crude product was purified using column chromatography (ethyl acetate/heptane 1:3) to give the title compound as a colourless oil, which slowly crystallised on standing (2.72 g, 10.2 mmol, 72%).

b) 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester, structure 13 of Scheme IV, where R¹ = 2-pyridyl, R² = 2-nitrophenyl, R³=R⁴=H.

To a solution of 1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester (2.72 g, 10.2 mmol) in dichloromethane (75 mL) was added at room temperature a solution of 2-nitrobenzenesulfonyl chloride (1.93 g, 10.2 mmol) in dichloromethane (75 mL). The mixture was stirred at room temperature for 24 hrs. The reaction mixture was concentrated and the crude product was purified using column chromatography (ethyl acetate/heptane 1:5 to 1:2) to give the title compound as a yellow solid (3.21 g, 7.65 mmol, 75%).

c) 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid, structure 14 of Scheme IV, where R¹ = 2-pyridyl, R² = 2-nitrophenyl, R³=R⁴=H.

To a suspension of 3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1H-indole-6-carboxylic acid methyl ester (3.0 g, 6.58 mmol) in dioxane (65 mL) was added a solution of LiOH.H₂O (1.66 g, 39.6 mmol) in water (65 mL). The reaction mixture was stirred overnight at 60°C. The mixture was then acidified to pH 6 by addition of 15%

aqueous HCl and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give a yellow powder. The product was recrystallised from heptane/ethyl acetate to give the title compound as yellow/orange crystals (2.47 g, 6.09 mmol, 93%)

5

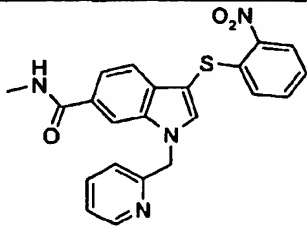
General method 7: amidation of 6-carboxyl indoles of structure **14** to give 6-carboxamideindoles of structure **15** (Scheme IV).

Under nitrogen atmosphere: to a solution of 3-(2-nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid (700 mg, 1.73 mmol) in dry CH₂Cl₂ (70 mL) was added DIPEA (0.9 mL, 5.2 mmol), TBTU (840 mg, 2.6 mmol) and dimethylamine hydrochloride (420 mg, 5.1 mmol). The reaction mixture was stirred overnight at room temperature and then poured into saturated aqueous NaHCO₃ (100 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄) and concentrated. The crude product was purified by column chromatography (ethyl acetate/MeOH 95:5) to afford compound **109** (540 mg, 1.25 mmol, 72%, yellow solid).

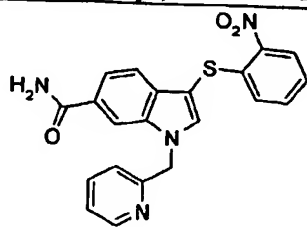
¹H-NMR (CDCl₃): δ 2.97 (s, 3H), 3.11 (s, 3H), 5.53 (s, 2H), 6.90 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.5 Hz), 6.95 (d, 1H, J = 7.6 Hz), 7.17-7.28 (m, 4H), 7.51 (d, 1H, J = 7.6 Hz), 7.54 (s, 1H), 7.61-7.66 (m, 2H), 8.28 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.5 Hz), 8.61 (d, 1H, J = 4.6 Hz).

20

The following compounds were prepared using general procedure 7:

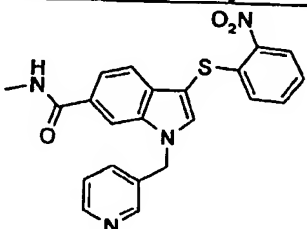
<p>Compound 110: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1<i>H</i>-indole-6-carboxylic acid methylamide, structure 15 of Scheme IV, where R¹ = 2-pyridyl, R² = 2-nitrophenyl, R³=R⁴=H, R⁸=H, R⁹=Me.</p>	
	<p>¹H-NMR (DMSO): δ 2.78 (d, 3H, J = 4.6 Hz), 5.70 (s, 2H), 6.88 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.5 Hz), 7.19 (d, 1H, J = 7.6 Hz), 7.30-7.37 (m, 2H), 7.41 (d, 1H, J = 8.4 Hz), 7.48-7.53 (m, 1H), 7.62 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.5 Hz), 7.79 (td, 1H, J₁ = 7.6 Hz, J₂ = 1.5 Hz), 8.13 (s, 1H), 8.20 (s, 1H), 8.28 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.5 Hz), 8.38 (q, 1H, J = 4.6 Hz), 8.55 (s, 1H, J = 4.6 Hz).</p>

Compound 111: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carboxylic acid amide, structure 15 of Scheme IV, where $R^1 = 2$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^8=R^9=H$.



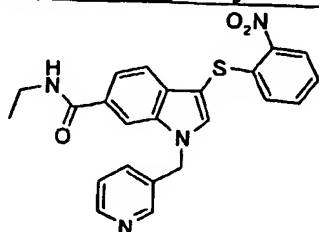
$^1\text{H-NMR}$ (DMSO): δ 5.70 (s, 2H), 6.88 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.21 (d, 1H, $J = 7.6$ Hz), 7.28-7.37 (m, 3H), 7.39 (d, 1H, $J = 7.6$ Hz), 7.48-7.53 (m, 1H), 7.66 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz), 7.79 (td, 1H, $J = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.93 (s, 1H), 8.17 (s, 1H), 8.20 (s, 1H), 8.26 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.55 (d, 1H, $J = 4.6$ Hz).

Compound 112: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid methylamide, structure 15 of Scheme IV, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^8=H$, $R^9=Me$. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.



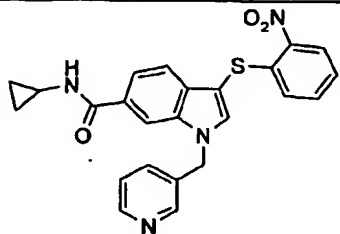
$^1\text{H-NMR}$ (DMSO): δ 2.80 (d, 3H, $J = 4.6$ Hz), 5.65 (s, 2H), 6.84 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33-7.42 (m, 3H), 7.46-7.51 (m, 1H), 7.62 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.68 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.28 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.41 (q, 1H, $J = 4.6$ Hz), 8.51 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 8.64 (d, 1H, $J = 3.0$ Hz).

Compound 113: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid ethylamide, structure 15 of Scheme IV, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3=R^4=H$, $R^8=H$, $R^9=Et$. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.



$^1\text{H-NMR}$ (DMSO): δ 1.13 (t, 3H, $J = 7.6$ Hz), 3.30 (q, 2H, $J = 7.6$ Hz), 5.66 (s, 2H), 6.83 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.33-7.41 (m, 3H), 7.46-7.51 (m, 1H), 7.64 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.67 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 2.2$ Hz), 8.19 (s, 1H), 8.26 (s, 1H), 8.27 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.45 (t, 1H, $J = 5.7$ Hz), 8.52 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.5$ Hz), 8.64 (d, 1H, $J = 3.0$ Hz).

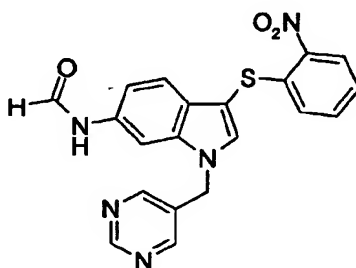
Compound 114: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1*H*-indole-6-carboxylic acid cyclopropylamide, structure **15** of Scheme IV, where $R^1 = 3$ -pyridyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^8 = H$, $R^9 = \text{cyclopropyl}$. 3-Picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.



$^1\text{H-NMR}$ (DMSO): δ 0.54-0.58 (m, 2H), 0.67-0.73 (m, 2H), 2.80-2.87 (m, 1H), 5.66 (s, 2H), 6.82 (d, 1H, $J = 7.6$ Hz), 7.33-7.41 (m, 3H), 7.46-7.50 (m, 1H), 7.61 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.67 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 8.17 (s, 1H), 8.25 (s, 1H), 8.28 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.42 (t, 1H, $J = 4.6$ Hz), 8.52 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.5$ Hz), 8.63 (d, 1H, $J = 3.0$ Hz).

Example 23

Compound 118: *N*-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide, structure **28** of Scheme VII, where $R^1 = 3,5$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $Z = H$



10 a) 6-Nitro-1-pyrimidin-5-ylmethyl-1*H*-indole

5-(Hydroxymethyl)pyrimidine (16.2 g, 147 mmol) was dissolved in 500 mL of CH_2Cl_2 and cooled to -40°C . MsCl (16.0 g, 140 mmol) was added at -40°C . The mixture was stirred for 1 hour allowing to reach -20°C . The solution was used as such.

6-Nitroindole-1*H*-indole (35.6 g, 220 mmol) was dissolved in 750 mL of DMF and NaH (50%, 12 g, 250 mmol) was added in portions and the mixture was stirred for 1 hour. The mixture was cooled to -40°C and the solution of the mesylate was added dropwise. The mixture was allowed to reach room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate (2x). The combined organic layers were washed with water (2x) and brine and dried over Na_2SO_4 . After concentration *in*

vacuo the material was purified by means of column chromatography (silica, heptane/ethyl acetate (1:1)→(1:4)) affording compound the title compound as a yellow solid (14 g, 55 mmol, 39%).

5 b) 1-Pyrimidin-5-ylmethyl-1*H*-indol-6-ylamine.

6-Nitro-1-pyrimidin-5-ylmethyl-1*H*-indole (4.1 g, 16.1 mmol) was dissolved in 100 mL of THF and 100 mL of isopropanol. Pd/C (2 g) was added and the mixture was stirred under an H₂-atmosphere (balloon) for 2 hours. The mixture was filtered over Celite and washed with ethyl acetate affording the title compound after concentration (3.5 g, 15.6 mmol, 97 %).

10 c) 1-Pyrimidin-5-ylmethyl-1*H*-indol-6-yl)-carbamic acid tert-butyl ester

1-Pyrimidin-5-ylmethyl-1*H*-indol-6-ylamine (5.5 g, 24.6 mmol) was dissolved in 100 mL of NMP and triethylamine (3.5 g, 35 mmol) and di-*tert*-butyl dicarbonate (7.0 g, 32 mmol) were added. The mixture was stirred overnight, quenched with NaHCO₃-sat and extracted with toluene (3x). The combined organic layers were washed with water (4x) and brine and dried over Na₂SO₄. Concentration of the layers afforded the title compound (3.1 g, 39%).

20 d) [3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-carbamic acid tert-butyl ester

1-Pyrimidin-5-ylmethyl-1*H*-indol-6-yl)-carbamic acid tert-butyl ester (3.1 g, 9.6 mmol) was dissolved in 150 mL of CH₂Cl₂ and 2-nitrobenzene sulfenylchloride (1.86 g, 9.8 mmol) was added. The mixture was stirred for 18 hours and quenched with NaHCO₃-sat and extracted with ethyl acetate (2x). The combined organic layers were washed with brine and dried over Na₂SO₄. The product was purified by means of column chromatography (silica, heptane / ethyl acetate (1:1) which gave the title compound as a yellow solid (3.8 g, 83 %).

30 e) N-[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-formamide

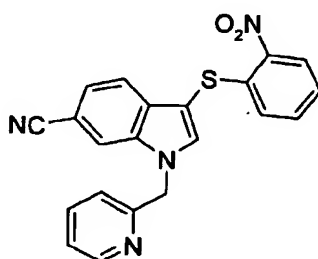
[3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1*H*-indol-6-yl]-carbamic acid tert-butyl ester (3.8 g, 8.0 mmol) was dissolved in 150 mL of formic acid and stirred for 4 hours. The solution was concentrated *in vacuo*. NaHCO₃-sat was added and the mixture was extracted with CH₂Cl₂ (2x) The combined organic layers were washed with brine and dried over Na₂SO₄. The solution was allowed to stand overnight. The formed solid

was filtered affording a mixture of compound **118** and structure **23** of Scheme VII, where $R^1 = 3,5\text{-pyrimidyl}$, $R^2 = 2\text{-nitrophenyl}$, $R^3 = R^4 = H$ (2.4 g).

Compound **118**: 1H NMR ($CDCl_3$ + drop MeOD) δ 5.47 (s, 2H), 6.91 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 6.99 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.19-7.23 (m, 1H), 7.27-7.31 (m, 1H), 7.33 (s, 1H), 7.42 (d, 1H, $J = 8.4$ Hz), 7.49 (s, 1H), 8.22 (d, 1H, $J = 1.9$ Hz), 8.27 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.66 (s, 2H), 9.16 (s, 1H).

Example 24

Compound **119**: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile, structure **3** of scheme I, where $R^1 = 2\text{-pyridyl}$, $R^2 = 2\text{-nitrophenyl}$, $R^3 = R^4 = H$, $R^5 = CN$.



a) To a solution of 1*H*-indole-6-carbonitrile (1.00 g, 7.04 mmol) in diethyl ether (50 mL) was added at rt 2-nitrobenzenesulfenyl chloride (1.34 g, 7.04 mmol) and the reaction mixture was stirred for 18 hrs. The mixture was concentrated and the crude product was purified using column chromatography (ethyl acetate/heptane 1:4 \rightarrow 4:1) to give 3-(2-Nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile (1.62 g, 5.49 mmol, 78%).

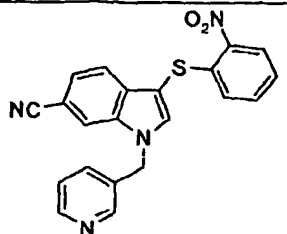
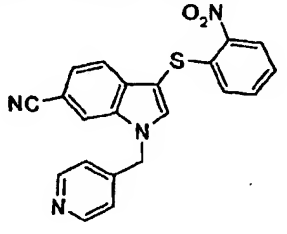
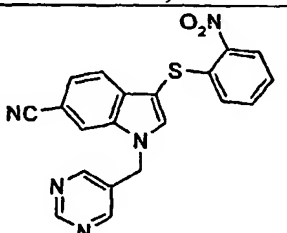
b) To a solution of 3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile (200 mg, 0.68 mmol) in DMF (5 mL) was added at 0 °C Cs_2CO_3 (442 mg, 1.36 mmol) and the mixture was stirred for 20 min. Subsequently 2-picolylchloride hydrochloride (112 mg, 0.68 mmol) was added and the mixture was stirred for 18 hrs at room temperature. Aqueous saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography to afford compound **119** (223 mg, 0.58 mmol, 85%).

1H NMR ($CDCl_3$) δ 5.54 (s, 2H), 6.86 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.04 (d, 1H, $J = 8.4$ Hz), 7.19-7.23 (m, 1H), 7.26-7.31 (m, 2H), 7.40 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$

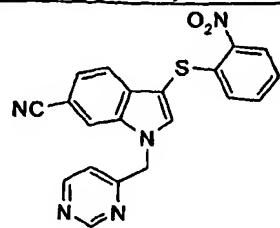
Hz), 7.59 (d, 1H, $J = 8.4$ Hz), 7.70 (td, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.76 (s, 1H), 7.78 (s, 1H), 8.29 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63 (d, 1H, $J = 3.0$ Hz).

According to **general method 3** the following compounds were prepared:

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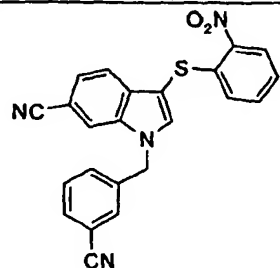
<p>Compound 121: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-3-ylmethyl-1<i>H</i>-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 3$-pyridyl, $R^2 = 2$-nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. CS_2CO_3 and DMF were used.</p> 	<p>1H NMR ($CDCl_3$) δ 5.46 (s, 2H), 6.82 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.21-7.25 (m, 1H), 7.27-7.31 (m, 1H), 7.34 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.6$ Hz), 7.43 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.49 (dt, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz), 7.61 (d, 1H, $J = 8.4$ Hz), 7.66 (s, 1H), 7.71 (s, 1H), 8.29 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.55 (d, 1H, $J = 3.0$ Hz), 8.64 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz).</p>
<p>Compound 122: 3-(2-Nitro-phenylsulfanyl)-1-pyridin-4-ylmethyl-1<i>H</i>-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 4$-pyridyl, $R^2 = 2$-nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$.</p> 	<p>1H NMR ($CDCl_3$) δ 5.46 (s, 2H), 6.84 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.04 (d, 2H, $J = 6.1$ Hz), 7.22-7.26 (m, 1H), 7.28-7.32 (m, 1H), 7.44 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.62 (d, 1H, $J = 8.4$ Hz), 7.64 (s, 1H), 7.68 (s, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63-8.65 (m, 2H). CS_2CO_3 and DMF were used.</p>
<p>Compound 123: 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-5-ylmethyl-1<i>H</i>-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 3,5$-pyrimidyl, $R^2 = 2$-nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. NaH and DMF were used.</p> 	<p>1H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.81 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.22-7.32 (m, 2H), 7.46 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 7.63 (d, 1H, $J = 8.4$ Hz), 7.68 (s, 1H), 7.70 (s, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 8.63 (s, 2H), 9.25 (s, 1H).</p>

Compound 124: 3-(2-Nitro-phenylsulfanyl)-1-pyrimidin-4-ylmethyl-1*H*-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 2,4$ -pyrimidyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. CS_2CO_3 and DMF were used.



1H NMR ($CDCl_3$) δ 5.52 (s, 2H), 6.86 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 6.97 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.1$ Hz), 7.22-7.32 (m, 2H), 7.44 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.62 (d, 1H, $J = 8.4$ Hz), 7.70 (s, 1H), 7.75 (s, 1H), 8.30 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.1$ Hz), 8.74 (d, 1H, $J = 4.6$ Hz), 9.24 (d, 1H, $J = 1.1$ Hz).

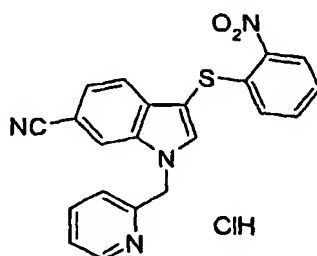
Compound 125: 1-(3-Cyano-benzyl)-3-(2-nitro-phenylsulfanyl)-1*H*-indole-6-carbonitrile, structure 3 of scheme I, where $R^1 = 3$ -cyanophenyl, $R^2 = 2$ -nitrophenyl, $R^3 = R^4 = H$, $R^5 = CN$. CS_2CO_3 and DMF were used.



1H NMR ($CDCl_3$) δ 5.48 (s, 2H), 6.83 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz), 7.21-7.26 (m, 1H), 7.30-7.35 (m, 1H), 7.38-7.42 (m, 3H), 7.45 (d, 1H, $J = 8.4$ Hz), 7.53 (d, 1H, $J = 7.6$ Hz), 7.64 (d, 1H, $J = 6.1$ Hz), 7.65 (d, 1H, $J = 3.7$ Hz), 7.66-7.69 (m, 1H), 8.30 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 1.1$ Hz).

Example 25

- 5 **Compound 120:** 3-(2-Nitro-phenylsulfanyl)-1-pyridin-2-ylmethyl-1*H*-indole-6-carbonitrile monohydrochloride



- 10 Concentrated hydrochloric acid (0.0225 ml) was added to a solution of compound 119 (0.093 g) in dioxane. The mixture was stirred for 20 min. and then concentrated under reduced pressure, to give compound 120 (0.096 g).

¹H NMR (MeOD) δ 6.01 (s, 2H), 6.98 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 7.28-7.32 (m, 1H), 7.36-7.41 (m, 1H), 7.48 (dd, 1H, J₁ = 7.6 Hz, J₂ = 1.1 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.93 (t, 1H, J = 6.1 Hz), 8.08 (s, 1H), 8.10 (s, 1H), 8.27 (dd, 1H, J₁ = 8.4 Hz, J₂ = 1.1 Hz), 8.44 (td, 1H, J₁ = 8.4 Hz, J₂ = 1.1 Hz), 8.85 (dd, 1H, J₁ = 6.1 Hz, J₂ = 1.9 Hz).

Compounds were tested for their Androgen Receptor activity in a transactivation assay and in a binding assay.

The (anti-)androgenic activity of test compounds (EC₅₀ and intrinsic activity) was determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human androgen receptor expression plasmid and a reporter plasmid in which the MMTV-promoter is linked to the luciferase reporter gene. The cell-line CHO-AR-pMMTV-LUC 1G12-A5-CA is described in Schoonen et al. (2000), Journal of Steroid Biochemistry and Molecular Biology 74(4):213-222. The antiandrogenic activity of a test compound was determined by the inhibition of the transactivation via the androgen receptor of the enzyme luciferase in the presence of 1 nM DHT (5α-dihydrotestosterone, 17β-hydroxy-5α-androstan-3-one). Intrinsic activity of antiandrogenic activity was determined in the presence of the reference antiandrogen 2-Hydroxy-2-methyl-N-(4-nitro-3-trifluoromethyl-phenyl)-propionamide (Hydroxyflutamide), and set at 100%. For androgenic activity, maximal intrinsic activity in the presence of 100 nM DHT was set at 100%. The results are presented in Table 4.

Table 4 Androgen receptor activity

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC ₅₀	ago efficacy	ant EC ₅₀	ant efficacy
1	S	2,5-difluorophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
2	S	2,fluoro,3-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
3	S	2-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
4	S	2-cyanophenyl	2-nitrophenyl	H	H	OMe	+	±	++	±
5	S	2-fluorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
6	S	2-methyl,3-nitrophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago efficacy	ant EC50	ant efficacy
7	S	2-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
8	S	2-nitrophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
9	S	2-pyridyl	2-nitrophenyl	H	H	OMe	+++	+	+++	±
10	S	2-pyridyl HCl salt	2-nitrophenyl	H	H	OMe	++	+	-	-
11	S	2-tetrahydropyranyl	2-nitrophenyl	H	H	OMe	++	+	-	-
12	S	2-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
13	S	3-(5-methylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	-	-
14	S	3,4-dichlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
15	S	3,5-dichlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
16	S	3,5-difluorophenyl	2-(hydroxymethylphenyl)	H	H	OMe	++	+	++	±
17	S	3,5-difluorophenyl	2-(N-methylbenzamide)	H	H	OMe	-	-	+	+
18	S	3,5-difluorophenyl	2-benzamide	H	H	OMe	++	+	++	±
19	S	3,5-difluorophenyl	2-benzoic acid methyl ester	H	H	OMe	+	+	-	-
20	S	3,5-difluorophenyl	2-cyanophenyl	H	H	OMe	++	++	-	-
21	S	3,5-difluorophenyl	2-methoxyphenyl	H	H	OMe	++			
22	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Br	++	++	-	-
23	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CF ₃	+++	++	-	-
24	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CH ₂ OH	++	++	-	-
25	S	3,5-difluorophenyl	2-nitrophenyl	H	H	Cl	+++	++	-	-
26	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CN	+++	++	-	-
27	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(1-pyrrolidinyl)	++	+	-	-
28	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO(4-morpholinyl)	++	+	-	-
29	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO[1-(4- methylpiperazinyl)]	++	++	-	-
30	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO ₂ H	+	+	-	-
31	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CO ₂ Me	+++	+	-	-
32	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONEt ₂	++	+	+	±
33	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONH ₂	+++	++	-	-
34	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (2-furanyl)	++	+	-	-
35	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ (3-pyridyl)	++	±	-	-
36	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ Nme ₂	++	+	-	-
37	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OH	+++	++	-	-
38	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH ₂ CH ₂ OMe	+++	++	-	-

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago efficacy	ant EC50	ant efficacy
39	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CO2Me	++	++	-	-
40	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2CONMe2	++	+	-	-
41	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2cPr	+++	+	-	-
42	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2iPr	++	+	-	-
43	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHCH2Ph	++	±	+	±
44	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHcPr	+++	+	-	-
45	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHEt	+++	++	-	-
46	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHiPr	++	+	++	±
47	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHMe	+++	+	-	-
48	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONHnPr	++	+	+	±
49	S	3,5-difluorophenyl	2-nitrophenyl	H	H	CONMe2	+++	+	-	-
50	S	3,5-difluorophenyl	2-nitrophenyl	H	H	F	++	++	-	-
51	S	3,5-difluorophenyl	2-nitrophenyl	F	H	H	+++	++	-	-
52	S	3,5-difluorophenyl	2-nitrophenyl	H	H	H	++	++	-	-
53	S	3,5-difluorophenyl	2-nitrophenyl	H	F	H	++	++	-	-
54	S	3,5-difluorophenyl	2-nitrophenyl	Cl	H	H	++	++	-	-
55	S	3,5-difluorophenyl	2-nitrophenyl	Me	H	H	++	+	-	-
56	S	3,5-difluorophenyl	2-nitrophenyl	H	OH	H	+++			
57	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NH2	+	+	-	-
58	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHAc	+++	++	-	-
59	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCF3	+++	+	-	-
60	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NO2	+++	++	-	-
61	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OH	+++			
62	SO2	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
63	S	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
64	SO	3,5-difluorophenyl	2-nitrophenyl	H	H	OMe	-	±	+	+
65	S	3,5-difluorophenyl	2-pyridyl	H	H	OMe	++	++	-	-
66	S	3,5-difluorophenyl	2-pyridyl-N-oxide	H	H	OMe	+	+	++	±
67	S	3-chlorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
68	S	3-cyanophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
69	S	3-fluoro,5- trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
70	S	3-fluoro,6- trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago EC50	ago efficacy	ant EC50	ant efficacy
71	S	3-fluorophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
72	S	3-methoxyphenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
73	S	3-methylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
74	S	3-nitrophenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
75	S	3-pyridyl	2-nitrophenyl	H	H	OMe	+++	++	-	-
76	S	3-trifluoromethyl,4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	-	-
77	S	3-trifluoromethyloxyphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
78	S	3-trifluoromethylphenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
79	S	4-(2-methylthiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
80	S	4-(3,5-dimethylisoxazolyl)	2-nitrophenyl	H	H	OMe	+	±	+	±
81	S	4-chlorophenyl	2-nitrophenyl	H	H	OMe	+	+	+++	+
82	S	4-cyanophenyl	2-nitrophenyl	H	H	OMe	++	+	-	-
83	S	4-fluorophenyl	2-nitrophenyl	H	H	OMe	++	++	-	-
84	S	4-methoxyphenyl	2-nitrophenyl	H	H	OMe	+	±	±	++
85	S	4-methylphenyl	2-nitrophenyl	H	H	OMe	+	+	-	±
86	S	4-morpholinyl	2-nitrophenyl	H	H	OMe	±	±	+	+
87	S	5-(2-chlorothiazolyl)	2-nitrophenyl	H	H	OMe	++	+	-	-
88	S	5-(2-chlorothiophenyl)	2-nitrophenyl	H	H	OMe	++	++	-	-
89	S	Cyclohexyl	2-nitrophenyl	H	H	OMe	++	+	+++	±
90	S	Phenyl	2-nitrophenyl	H	H	H	+	+	-	-
91	S	Phenyl	2-nitrophenyl	H	OMe	H	-	-	±	++
92	S	Phenyl	2-nitrophenyl	H	H	OMe	+++	++	-	-

note 1: EC50 scale: +++ <5 nM; ++ between 5 and 100 nM; + <1000 nM; ± between 1000 and 10000 nM; - >10000 nM

note 2: efficacy scale (maximal intrinsic activity, i.e. intrinsic activity observed in the presence of 100 nM DHT, was set at 1.00): ++ ≥0.80; + between 0.50 and 0.80; ± between 0.20 and 0.50; - <0.20

The androgenic activity (EC50, potency, and efficacy) of the compounds in Table 5 was determined in an *in vitro* bioassay of Chinese hamster ovary (CHO) cells stably transfected with the human androgen receptor expression plasmid and a reporter

plasmid in which the MMTV promotor is linked to the luciferase reporter gene. The cell line CHO-AR-pMMTV-LUC 1G12-A5-CA is described in Schoonen *et al.* (J. Steroid Biochem. Molec. Biol. 2002; 74: 213-222). The androgen receptor activity of compounds was determined in the presence of 0.1 $\mu\text{mol/l}$ onapristone. The maximal efficacy in the presence of 100 nmol/l DHT was set as 100%. The potencies are expressed as percentage of DHT activity.

Table 5 Androgen receptor activity

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago potency	ago efficacy
93	S	4-pyridyl	2-nitrophenyl	H	H	OMe	±	+
94	S	3,4,5-trifluorophenyl	2-nitrophenyl	H	H	OMe	+	++
95	S	2,3,5-trifluorophenyl	2-nitrophenyl	H	H	OMe	±	++
96	S	4-chloro-3-pyridyl	2-nitrophenyl	H	H	OMe	±	±
97	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCH ₂ F	+	++
98	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOCHF ₂	++	+
99	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHCOEt	±	+
100	S	2-pyridyl	2-nitrophenyl	H	H	NHCOCH ₂ F	+	++
101	S	2-pyridyl	2-nitrophenyl	H	H	NHCOMe	+	+
102	S	2-pyridyl	2-nitrophenyl	H	H	NHCOEt	+	+
103	S	3-pyridyl	2-nitrophenyl	H	H	NHCOMe	+	+
104	S	3-pyridyl	2-nitrophenyl	H	H	NHCOCH ₂ F	+	-
105	S	3-pyridyl	2-nitrophenyl	H	H	NHCOEt	+	±
106	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO ₂ Me	+	++
107	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO ₂ -(3-thiophene)	+	++
108	S	3,5-difluorophenyl	2-nitrophenyl	H	H	NHSO ₂ -(1-Me-4-imidazolyl)	+	++
109	S	2-pyridyl	2-nitrophenyl	H	H	CONMe ₂	+	++
110	S	2-pyridyl	2-nitrophenyl	H	H	CONHMe	+	+
111	S	2-pyridyl	2-nitrophenyl	H	H	CONH ₂	±	±
112	S	3-pyridyl	2-nitrophenyl	H	H	CONHMe	+	±
113	S	3-pyridyl	2-nitrophenyl	H	H	CONHEt	+	+
114	S	3-pyridyl	2-nitrophenyl	H	H	CONHcyclopropyl	+	++
115	S	3,5-pyrimidyl	2-nitrophenyl	H	H	OMe	++	+
116	S	2,4-pyrimidyl	2-nitrophenyl	H	H	OMe	+	+

Cpd. number	X	R ¹	R ²	R ³	R ⁴	R ⁵	ago potency	ago efficacy
117	S	2,5-pyrazyl	2-nitrophenyl	H	H	OMe	+	+
118	S	3,5-pyrimidyl	2-nitrophenyl	H	H	NHCHO	++	+
119	S	2-pyridyl	2-nitrophenyl	H	H	CN	++	++
120	S	2-pyridyl HCl salt	2-nitrophenyl	H	H	CN	++	++
121	S	3-pyridyl	2-nitrophenyl	H	H	CN	+	++
122	S	4-pyridyl	2-nitrophenyl	H	H	CN	+	+
123	S	3,5-pyrimidyl	2-nitrophenyl	H	H	CN	++	++
124	S	2,4-pyrimidyl	2-nitrophenyl	H	H	CN	++	++
125	S	3-cyanophenyl	2-nitrophenyl	H	H	CN	+	++

note 1: potency scale: ++ >5%; + between 1% and 5%; ± between 0.1% and 1%.

note 2: efficacy scale (maximal intrinsic activity, i.e. intrinsic activity observed in the presence of 100 nM DHT, was set at 1.00): ++ ≥0.80; + between 0.50 and 0.80; ±

5 between 0.20 and 0.50; - <0.20.

10 Determination of competitive binding to cytoplasmic human androgen receptor from recombinant CHO cells is used to estimate the relative binding affinity (RBA) of a test compound for androgen receptors present in the cytosol prepared of the recombinant CHO cell-line, CHO-AR-pMMTV-LUC 1G12-A5-CA.

Compound 63 and compound 92 were tested in this binding assay and both compounds were found to have a relative binding affinity >1% relative to DHT.